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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
G01N 33/53

A1

(11) International Publication Number: WO 98/34111

(43) International Publication Date: 6 August 1998 (06.08.98)

(21) International Application Number: PCT/US97/22206

(22) International Filing Date: 5 December 1997 (05.12.97)

(30) Priority Data:
08/795,893 4 February 1997 (04.02.97) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: TRICYCLIC TETRAHYDROQUINOLINE DERIVATIVES AND TRICYCLIC TETRAHYDROQUINOLINE COMBINATORIAL LIBRARIES

(57) Abstract

The present invention relates to novel tricyclic tetrahydroquinoline compounds, combinatorial libraries containing mixtures of two or more such compounds, and also relates to the generation of such libraries.

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TRICYCLIC TETRAHYDROQUINOLINE DERIVATIVES AND TRICYCLIC TETRAHYDROQUINOLINE COMBINATORIAL LIBRARIES

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates generally to the synthesis of heterocyclic compounds based on the tricyclic tetrahydroquinoline ring. More specifically, the invention provides novel tricyclic tetrahydroquinolines as well as novel libraries comprised of such compounds.

BACKGROUND INFORMATION

The process of discovering new therapeutically active compounds for a given indication involves the screening of all compounds from available compound collections. From the compounds tested one or more structure(s) is selected as a promising lead. A large number of related analogs are then synthesized in order to develop a structure-activity relationship and select one or more optimal compounds. With traditional one-at-a-time synthesis and biological testing of analogs, this optimization process is long and labor intensive. Adding significant numbers of new structures to the compound collections used in the initial screening step of the discovery and optimization process cannot be accomplished with traditional one-at-a-time synthesis methods, except over a time frame of months or even years. Faster methods are needed that allow for the preparation of up to thousands of related compounds in a matter of days or a few weeks. This need is particularly evident when it

comes to synthesizing more complex compounds, such as tricyclic tetrahydroquinolines.

Solid-phase techniques for the synthesis of peptides have been extensively developed and combinatorial libraries of peptides have been generated with great success. During the past four years there has been substantial development of chemically synthesized combinatorial libraries (SCLs) made up of peptides. The preparation and use of synthetic peptide combinatorial libraries has been described, for example, by Dooley in U.S. Patent 5,367,053, Huebner in U.S. Patent 5,182,366, Appel et al. in WO PCT 92/09300, Geysen in published European Patent Application 0 138 855 and Pirrung in U.S. Patent 5,143,854. Such SCLs provide the efficient synthesis of an extraordinary number of various peptides in such libraries and the rapid screening of the library which identifies lead pharmaceutical peptides.

Combinatorial approaches have recently been extended to "organic," or non-peptide, libraries. The organic libraries to the present, however, are of limited diversity and generally relate to peptidomimetic compounds; in other words, organic molecules that retain peptide chain pharmacophore groups similar to those present in the corresponding peptide.

Combinatorial chemical methods have been applied to a limited number of heterocyclic compounds, as described, for example, in U.S. Patent 5,288,514 to Ellman, U.S. Patent 5,324,483 to Cody et al. and Goff and Zuckermann, J. Org. Chem., 60:5748-5749 (1995). Additionally, there is U.S. Patent 5,549,974 to Holmes and U.S. Patent 5,506,337 to Summerton and Weller. However, the heterocyclic libraries to date contain compounds of limited diversity and complexity.

Five 3,4-cyclopentenyl substituted tetrahydroquinolines have been prepared by classical organic synthesis as described, for example in Grieco and Bahsas, Tetrahedron Letters, 29:5855-5858 (1988). However, their procedures are limited to use of one equivalent of aldehyde for formation of the imine intermediate in order to limit the hetero Diel-Alder reaction with cyclopentadiene and thus avoid a double hetero Diels-Alder reaction. Gregoire et al., Tetrahedron Letters, 32:7099 (1991), has also described classical synthesis of the cyclopentadiene hetero Diels-Alder reaction to prepare a series of nine aza-steroid derivatives. There remains a need, however, to prepare these compounds in libraries of substantial molecular diversity.

Patent application WO 94/08051 discloses the reaction of ether-linked aldehyde-derived imines with dihydrofuran under Lewis acid catalysis. However, the library described therein was limited to 108 compounds. Moreover, while lanthanide triflates have been reported to effect the preparation of tricyclic tetrahydroquinolines they are expensive and the reaction scope where they have been employed is very limited. See for example, Kobayashi et al., Chemistry Letters, 423 (1995).

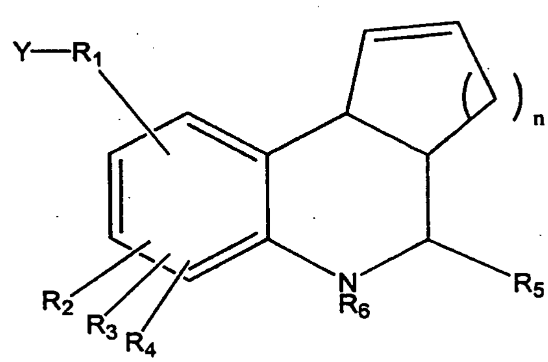
Substituent limitations have been overcome for mixtures of peptides and peptidomimetics through the use of solid phase techniques versus solution-phase. An important step in the development of solid-phase techniques was the discovery of methods to identify active individual compounds from soluble mixtures of large numbers of compounds, as described, for example, by Rutter in U.S. Patent 5,010,175 and Simon in WO PCT 91/19735. These soluble mixture methods, however, have rarely been applied to the syntheses of complex heterocyclic structures. There exists a need to develop more complex "organic" libraries based on heterocyclic medicinal compounds which would require less time and effort in the synthesis and

testing needed to bring an organic pharmaceutical product to fruition. In short, improved methods for generating therapeutically useful heterocyclic compounds, such as tricyclic tetrahydroquinoline derivatives, are desired.

This invention satisfies these needs and provides related advantages as well. The present invention overcomes the known limitations to classical organic synthesis of tricyclic tetrahydroquinolines and as well as the shortcomings of combinatorial chemistry with heterocycles. The present invention combines the techniques of solid-phase synthesis of heterocycles and the general techniques of synthesis of combinatorial libraries to prepare new tricyclic tetrahydroquinoline compounds.

SUMMARY OF THE INVENTION

The present invention relates to novel tricyclic tetrahydroquinoline compounds of the following formula, libraries containing at least two or more such compounds, and to the generation of such combinatorial libraries composed of such compounds:



Formula I

wherein R^1, R^2, R^3, R^4, R^5, R^6, n and Y have the meanings provided below.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides Reaction Scheme I for preparing the tricyclic tetrahydroquinoline compounds of the present invention.

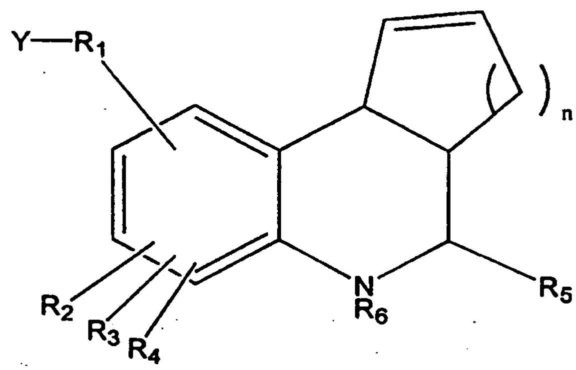
Figure 2 shows a more detailed reaction scheme, Reaction Scheme II, for the preparation of the subject tricyclic tetrahydroquinolines and libraries containing the same.

Figure 3 provides Reaction Scheme III for the preparation of libraries and compounds containing alternatively branched tricyclic tetrahydroquinolines at the R^8 position.

Figure 4 provides Reaction Scheme IV for the preparation of libraries and compounds containing alternatively substituted tricyclic tetrahydroquinolines at the R^6 position.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel derivatives and libraries of novel derivatives of variously substituted tricyclic tetrahydroquinoline compounds of Formula I:



Formula I

In the above Formula I:

R^1 is absent or present and, when present, is C_1 to C_{10} alkylene, C_1 to C_{10} substituted alkylene, C_2 to C_{10} alkenyl, C_2 to C_{10} substituted alkenyl, C_2 to C_{10} alkynyl, C_2 to C_{10} substituted alkynyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, phenylene, substituted phenylene, naphthyl, substituted naphthyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, heterocyclic ring, substituted heterocyclic ring, heteroaryl ring, substituted heteroaryl ring, amino, (monosubstituted)amino, a group of the formula: -$CH_2C(O)NH$- or a group of the formula:

$$-(CH_2)_p-Ar-(CH_2)_q-$$

wherein p and q are independently selected from a number 0 to 6, wherein both are not 0; and Ar is an aryl group selected from the group consisting of phenyl, substituted phenyl, heteroaryl ring or substituted heteroaryl ring,

R^2, R^3, and R^4 are, independently, a hydrogen atom, halo, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_2 to C_{10} alkynyl, C_1 to C_{10} substituted alkyl, C_2 to C_{10} substituted alkenyl, C_2 to C_{10} substituted alkynyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyloxy, C_1 to C_7 acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, C_1 to C_4 alkylthio, C_1 to C_4 substituted alkylthio, C_1 to C_4 alkylsulfonyl, C_1 to C_4 substituted alkylsulfonyl, C_1 to C_4 alkylsulfoxide, C_1 to C_4 substituted alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl or substituted phenylsulfonyl;

R^5 is hydrogen, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, C_2 to C_{10} alkenyl, C_2 to C_{10} substituted alkenyl, C_2 to C_{10} alkynyl, C_2 to C_{10} substituted alkynyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, carboxy, protected carboxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, heterocyclic ring, substituted heterocyclic ring, heteroaryl ring or substituted heteroaryl ring;

R^6 is a hydrogen atom, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_4 alkylsulfonyl, C_1 to C_4 substituted alkylsulfonyl, C_1 to C_6 alkylaminocarbonyl, C_1 to C_6 substituted alkylaminocarbonyl, phenylaminocarbonyl, or substituted phenylaminocarbonyl;

n is 1 to 3; and

Y is CO_2H, OH, SH, NHR^7, $C(O)NHR^7$, CH_2OH, CH_2NH_2, or CH_2NHR^7, wherein R^7 is a hydrogen atom, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, or a functionalized resin, providing that when Y is CO_2H that R^1 is not absent and R^5 is not phenyl, and more preferably, Y is CO_2H, NHR^7 or $C(O)NHR^7$, wherein R^7 is a hydrogen atom, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, or a functionalized resin, providing that when Y is CO_2H that R^1 is not absent and R^5 is not phenyl.

For R^1 defined above, p and q are independently selected from a number 0 to 6. Preferably, p and q are independently selected from 0 to 4 and, more preferably, from 0 to 3.

In one embodiment of the invention the tricyclic tetrahydroquinoline compounds and libraries containing the same are wherein:

R^1 is absent or present and, when present, is C_1 to C_{10} alkylene, C_1 to C_{10} substituted alkylene, phenylene, substituted phenylene, or a group of the formula: $-CH_2C(O)NH-$;

R^2, R^3, and R^4 are, independently, selected from a hydrogen atom, halo, hydroxy, protected hydroxy, nitro, C_1 to C_{10} alkyl, C_1 to C_7 alkoxy, or cyclic C_2 to C_7 alkylene;

R^5 is hydrogen atom, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, C_2 to C_7 alkenyl, C_2 to C_7 substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_5 to C_7 cylcoalkenyl, C_5 to C_7 substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, heteroaryl, substituted heteroaryl, C_1 to C_7 acyl, substituted acyl, carboxy or protected carboxy;

R^6 is a hydrogen atom;

n is 1 to 2; and

Y is C(O)NHR^7, wherein R^7 is a hydrogen atom or a functionalized resin.

In another embodiment, the tricyclic tetrahydroquinoline compounds and libraries containing the same are wherein:

R^1 is absent or present and, when present, is -CH_2NHCO- or -CH_2CH(NHR^8)-, wherein R^8 is selected from a hydrogen atom, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, C_2 to C_{10} alkenyl, C_2 to C_{10} substituted alkenyl, C_2 to C_{10} alkynyl, C_2 to C_{10} substituted alkynyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, aminocarbonyl, protected aminocarbonyl, (monosubstituted)aminocarbonyl, protected (monosubstitituted)aminocarbonyl, (disubstituted)aminocarbonyl, C_1 to C_7

alkylsulfonyl, C_7 to C_{12} phenylalkylsulfonyl, phenylsulfonyl or substituted phenylsulfonyl;

R^2, R^3, and R^4 are each, independently, a hydrogen atom, nitro, hydroxy, halo, C_1 to C_{10} alkyl, C_1 to C_6 alkoxy, or cyclic C_2 to C_7 alkylene;

R^5 is a hydrogen atom, carboxy, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, C_2 to C_{10} alkenyl, C_2 to C_{10} substituted alkenyl, C_3 to C_8 cycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, heterocyclic ring, substituted heterocyclic ring, heteroaryl ring or substituted heteroaryl ring;

n is equal to 1;

R^6 is a hydrogen atom; and

Y is $C(O)NH_2$ or C(O)NH bound to a functionalized resin.

In yet another embodiment, as exemplified in Example 1 below,

R^1 is absent or CH_2NHCO;

R^2, R^3, and R^4 are each, independently, a hydrogen atom, hydroxy, fluoro, chloro, bromo, iodo, methyl, methoxy, nitro or -CH=CH-CH=CH- fused to adjacent positions;

R^5 is a hydrogen atom, phenyl, chloromethyl, cyclohexanyl, d,l- 1,2-(dihydroxy)ethyl, carboxy, acetyl, 2-hydroxyphenyl, tribromomethyl, trimethylacetyl, 1-methyl-2-pyrrolyl, 1-napthyl, 2,3,4-trifluorophenyl, 2,3,5-trichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-

difluorophenyl, 2,5-dimethylphenyl, 2,6-difluorophenyl, 2-bromophenyl, 2-chloro-5-nitrophenyl, 2-chloro-6-fluorophenyl, 2-cyanophenyl, 2-ethylbutyryl, 2-fluorophenyl, 2-(2-oxymethylenecarboxy)phenyl, 2-methoxy-1-naphthyl, 2-nitro-5-chlorophenyl, 2-nitrophenyl, 2-pyridinyl, 3,4-(methylenedioxy)-6-nitrophenyl, 3,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-dichlorophenyl, 3-(3,4-dichlorophenoxy)phenyl, 3-bromo-4-fluorophenyl, 3-bromophenyl, 3-carboxyphenyl, 3-cyanophenyl, 3-fluorophenyl, 3-chromonyl, 3-furyl, 3-hydroxyphenyl, 3-nitro-4-chlorophenyl, 3-nitrophenyl, 3-phenoxyphenyl, 2-phenylpropyl, 3-pyridinyl, 4-bromo-2-thiophene-yl, 4-bromophenyl, 4-carboxyphenyl, 4-cyanophenyl, 4-fluorophenyl, 4-nitrophenyl, 4-pyridinyl, 4-quinolinyl, 5-bromo-2-hydroxyphenyl, 5-nitro-2-furyl, 5-norbornene-2-yl, 6-methyl-2-pyridinyl, 9-ethyl-3-carbazolyl, 1,2-dimethylbutyryl, 1,1-dimethyl-3-butenyl, 3-methoxy-2-nitro-phenyl, 3-hydroxy-4-nitrophenyl, 1-methylpropyl, 1-methylbutyl, 4-chloro-3-nitrophenyl, 4-(trifluoromethyl)phenyl, 1-methyldecanyl, or β-phenylcinnaminyl;

R^6 is a hydrogen atom;

n is 1; and

Y is $C(O)NH_2$ or C(O)NH bound to a functionalized resin.

In a further preferred embodiment, exemplified in Example 2,

R^1 is $CH_2CH(NHR^8)$ wherein R^8 is acetyl, butyryl, cyclobutanecarbonyl, cycloheptanecarbonyl, 4-cyclohexanebutyryl, cyclohexanecarbonyl, 3-cyclohexanepropionyl, cyclohexylacetyl, cyclopentanecarbonyl, cyclopentylacetyl, hydrocinnamyl, isobutyryl, isovaleryl, octanoyl,

propionyl, tert-butylacetyl, trimethylacetyl, 1-adamantaneacetyl, 4-methyl-1-cyclohexanecarbonyl, 4-methylcyclohexaneacetyl, 4-methylvaleryl, 2-ethyl-2-hexenoyl, 2-ethylbutyryl, 2-ethylhexanoyl, 2-methylbutyryl, 2-methylcyclopropanecarbonyl, 2-norbornaneacetyl, 2-phenylbutyryl, 2-propylpentanoyl, 3,3,3-triphenylpropionyl, 3,3-diphenylpropionyl, 4-tert-butyl-cyclohexanecarbonyl, 3,5,5-trimethylhexanoyl, 5-phenylvaleryl, 3-(2-methoxyphenyl)propionyl, 3-(3,4,5-trimethoxyphenyl)propionyl, 3-(3,4-dimethoxyphenyl)propionyl, heptanoyl, 3-cyclopentylpropionyl, formyl, lauryl, 3-methylvaleryl, 3-phenylbutyryl, α-cyclohexylphenylacetyl, α-methylcinnamyl, crotonyl, ethoxyacetyl, 4-chlorocinnamyl, 4-ethoxyphenylacetyl, m-tolylacetyl, methoxyacetyl, p-tolylacetyl, phenoxyacetyl, phenylacetyl, tiglyl, trans-3-hexenoyl, trans-cinnamyl, trans-styrylacetyl, triphenylacetyl, 4-fluorophenylacetyl, vinylacetyl, (2,5-dimethoxyphenyl)acetyl, (2-naphthoxy)acetyl, (3,4-dimethoxyphenyl)acetyl, (α-α-α-trifluoro-m-tolyl)acetyl, (methylthio)acetyl, 1-(4-chlorophenyl)-1-cyclopentanecarbonyl, 1-naphthylacetyl, 1-phenyl-1-cyclopropanecarbonyl, 4-isobutyl-α-methylphenylacetyl, 4-methoxyphenylacetyl, 2,4-hexadienoyl, 2-(trifluoromethyl)-cinnamyl, 2-chloro-4-fluorophenylacetyl, 2-naphthylacetyl, 3,4,5-trimethoxycinnamyl, 3,4-dichlorophenylacetyl, 3,4-dimethylbenzoyl, 3,4,5-trimethoxyphenylacetyl, 3-benzoylpropionyl, 3-bromophenylacetyl, 3-fluorophenylacetyl, 3-methoxyphenylacetyl, 3-thiopheneacetyl, 4-biphenylacetyl, 4-bromophenylacetyl, α,α,α-trifluoro-m-toluyl, α,α,α-trifluoro-o-toluyl, benzoyl, niflumyl, o-anisyl, o-toluyl, piperonylyl, 1-napthoyl, 2,3-dichlorobenzoyl, 2,3-dimethoxybenzoyl, 2,4-dichlorobenzoyl, 2,4-difluorobenzoyl, 2,4-dimethoxybenzoyl, 2,4-dimethylbenzoyl, 2,5-dichlorobenzoyl, 2,5-dimethylbenzoyl, 2,6-dychlorobenzoyl, 2,6-difluorobenzoyl, 2,6-dimethoxybenzoyl, 2-

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R^2, R^3, and R^4 are each, independently, a hydrogen atom;

R^5 is a carboxy, 1-napthyl, 2,3,4-trifluorophenyl, 2,3,5-trichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-difluorophenyl, 2,5-dimethylphenyl, 2,6-difluorophenyl, 2-bromophenyl, 2-chloro-5-nitrophenyl, 2-fluorophenyl, 3,4-(methylenedioxy)-6-nitrophenyl, 3,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-dichlorophenyl, 3-cyanophenyl, 3-fluorophenyl, 3-chromonyl, 3-nitro-4-chlorophenyl, 3-

phenoxyphenyl, 4-cyanophenyl, 4-pyridinyl, 3-methoxy-2-nitrophenyl, or 3-hydroxy-4-nitrophenyl;

R^6 is a hydrogen atom;

n is 1; and

Y is $C(O)NH_2$ or C(O)NH bound to a functionalized resin.

In an alternative embodiment,

R^1 is absent or present and, when present, is $-CH_2NHCO-$ or $CH_2CH(NHR^8)$ wherein R^8 is acetyl, butyryl, cyclobutanecarbonyl, cycloheptanecarbonyl, 4-cyclohexanebutyryl, cyclohexanecarbonyl, 3-cyclohexanepropionyl, cyclohexylacetyl, cyclopentanecarbonyl, cyclopentylacetyl, hydrocinnamyl, isobutyryl, isovaleryl, octanoyl, propionyl, tert-butylacetyl, trimethylacetyl, 1-adamantaneacetyl, 4-methyl-1-cyclohexanecarbonyl, 4-methylcyclohexaneacetyl, 4-methylvaleryl, 2-ethyl-2-hexenoyl, 2-ethylbutyryl, 2-ethylhexanoyl, 2-methylbutyryl, 2-methylcyclopropanecarbonyl, 2-norbornaneacetyl, 2-phenylbutyryl, 2-propylpentanoyl, 3,3,3-triphenylpropionyl, 3,3-diphenylpropionyl, 4-tert-butyl-cyclohexanecarbonyl, 3,5,5-trimethylhexanoyl, 5-phenylvaleryl, 3-(2-methoxyphenyl)propionyl, 3-(3,4,5-trimethoxyphenyl)propionyl, 3-(3,4-dimethoxyphenyl)propionyl, heptanoyl, 3-cyclopentylpropionyl, formyl, lauryl, 3-methylvaleryl, 3-phenylbutyryl, α-cyclohexylphenylacetyl, α-methylcinnamyl, crotonyl, ethoxyacetyl, 4-chlorocinnamyl, 4-ethoxyphenylacetyl, m-tolylacetyl, methoxyacetyl, p-tolylacetyl, phenoxyacetyl, phenylacetyl, tiglyl, trans-3-hexenoyl, trans-cinnamyl, trans-styrylacetyl, triphenylacetyl, 4-

fluorophenylacetyl, vinylacetyl, (2,5-dimethoxyphenyl)acetyl, (2-naphthoxy)acetyl, (3,4-dimethoxyphenyl)acetyl, (α-α-α-trifluoro-m-tolyl)acetyl, (methylthio)acetyl, 1-(4-chlorophenyl)-1-cyclopentanecarbonyl, 1-naphthylacetyl, 1-phenyl-1-cyclopropanecarbonyl, 4-isobutyl-α-methylphenylacetyl, 4-methoxyphenylacetyl, 2,4-hexadienoyl, 2-(trifluoromethyl)-cinnamyl, 2-chloro-4-fluorophenylacetyl, 2-naphthylacetyl, 3,4,5-trimethoxycinnamyl, 3,4-dichlorophenylacetyl, 3,4-dimethylbenzoyl, 3,4,5-trimethoxyphenylacetyl, 3-benzoylpropionyl, 3-bromophenylacetyl, 3-fluorophenylacetyl, 3-methoxyphenylacetyl, 3-thiopheneacetyl, 4-biphenylacetyl, 4-bromophenylacetyl, α,α,α-trifluoro-m-toluyl, α,α,α-trifluoro-o-toluyl, benzoyl, niflumyl, o-anisyl, o-toluyl, piperonylyl, 1-napthoyl, 2,3-dichlorobenzoyl, 2,3-dimethoxybenzoyl, 2,4-dichlorobenzoyl, 2,4-difluorobenzoyl, 2,4-dimethoxybenzoyl, 2,4-dimethylbenzoyl, 2,5-dichlorobenzoyl, 2,5-dimethylbenzoyl, 2,6-dychlorobenzoyl, 2,6-difluorobenzoyl, 2,6-dimethoxybenzoyl, 2-bromobenzoyl, 2-chloro-4,5-difluorobenzoyl, 2-chlorobenzoyl, 2-ethoxybenzoyl, 2-fluorobenzoyl, 2-napthoyl, 3,4,5-triethoxybenzoyl, 3,4,5-trimethoxybenzoyl, 3,4-dichlorobenzoyl, 3,4-difluorobenzoyl, 3,4-dimethoxybenzoyl, 3,5-bis(trifluoromethyl)benzoyl, 5-bromo-2-chlorobenzoyl, 3,5-dimethyl-p-anisyl, 3-bromobenzoyl, 3-chlorobenzoyl, 3-cyanobenzoyl, 3-(dimethylamino)benzoyl, 3-fluoro-4-methylbenzoyl, 3-fluorobenzoyl, 3-iodo-4-methylbenzoyl, 3-phenoxybenzoyl, 4-chloro-o-anisyl, α,α,α-trifluoro-p-toluyl, 4-cyanobenzoyl, 4-(dimethylamino)benzoyl, 4-ethoxybenzoyl, isonicotinyl, 4-ethylbenzoyl, m-anisyl, m-toluyl, nicotinyl, p-anisyl, p-toluyl, picolinyl, pyrrole-2-carbonyl, 4-fluorobenzoyl, 4-isopropoxybenzoyl, tetrahydro-2-furoyl, tetrahydro-3-furoyl, trans-3-(3-pyridyl)acrylyl, xanthene-9-carbonyl, (4-pyridylthio)acetyl, (phenylthio)acetyl, 4-iodobenzoyl, 4-

isopropylbenzoyl, 2-furoyl, 2-pyrazinecarbonyl, 2-thiopheneacetyl, 2-thiophenecarbonyl, 5-bromonicotinyl, 3,5-dichlorobenzoyl, 6-chloronicotinyl, 3,5-dimethoxybenzoyl, 3,5-dimethylbenzoyl, chromone-2-carbonyl, 1-isoquinolinecarbonyl, 3-methyl-2-thiophene-yl, 4'-ethyl-4-biphenylcarbonyl, 4-(diethylamino)benzoyl, 4-benzoylbenzoyl, 4-biphenylcarbonyl, 4-bromobenzoyl, 4-butylbenzoyl, or 4-chlorobenzoyl;

R^2, R^3, and R^4 are each, independently, a hydrogen atom, hydroxy, fluoro, chloro, bromo, iodo, methyl, methoxy, nitro or -CH=CH-CH=CH- fused to adjacent positions;

R^5 is a hydrogen atom, phenyl, chloromethyl, cyclohexanyl, d,l- 1,2-(dihydroxy)ethyl, carboxy, acetyl, 2-hydroxyphenyl, tribromomethyl, trimethylacetyl, 1-methyl-2-pyrrolyl, 1-napthyl, 2,3,4-trifluorophenyl, 2,3,5-trichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-difluorophenyl, 2,5-dimethylphenyl, 2,6-difluorophenyl, 2-bromophenyl, 2-chloro-5-nitrophenyl, 2-chloro-6-fluorophenyl, 2-cyanophenyl, 2-ethylbutyryl, 2-fluorophenyl, 2-(2-oxymethylenecarboxy)phenyl, 2-methoxy-1-naphthyl, 2-nitro-5-chlorophenyl, 2-nitrophenyl, 2-pyridinyl, 3,4-(methylenedioxy)-6-nitrophenyl, 3,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-dichlorophenyl, 3-(3,4-dichlorophenoxy)phenyl, 3-bromo-4-fluorophenyl, 3-bromophenyl, 3-carboxyphenyl, 3-cyanophenyl, 3-fluorophenyl, 3-chromonyl, 3-furyl, 3-hydroxyphenyl, 3-nitro-4-chlorophenyl, 3-nitrophenyl, 3-phenoxyphenyl, 2-phenylpropyl, 3-pyridinyl, 4-bromo-2-thiophene-yl, 4-bromophenyl, 4-carboxyphenyl, 4-cyanophenyl, 4-fluorophenyl, 4-nitrophenyl, 4-pyridinyl, 4-quinolinyl, 5-bromo-2-hydroxyphenyl, 5-nitro-2-furyl, 5-norbornene-2-yl, 6-methyl-2-pyridinyl, 9-ethyl-3-carbazolyl, 1,2-dimethylbutyryl, 1,1-dimethyl-3-butenyl, 3-methoxy-2-nitro-phenyl, 3-hydroxy-4-nitrophenyl,

1-methylpropyl, 1-methylbutyl, 4-chloro-3-nitrophenyl, 4-(trifluoromethyl)phenyl, 1-methyldecanyl, or β-phenylcinnaminyl;

R^6 is nalidixoyl, 2-phenyl-4-quinolinecarboxy, 2-pyrazinecarboxy, niflumoyl, 4-nitrophenylacetyl, 4-(4-nitrophenyl)butyroyl, (3,4-dimethoxyphenyl)acetyl, 3,4-(methylenedioxy)phenylacetyl, 4-nitrocinnamoyl, 3,4-(methylenedioxy)cinnamoyl, 3,4,5-trimethoxycinnamoyl, benzoyl, 2-chlorobenzoyl, 2-nitrobenzoyl, 2-(p-toluoyl)benzoyl, 2,4-dinitrophenylacetyl, 3-(3,4,5-trimethoxyphenyl)-propionyl, 4-biphenylacetyl, 1-napthylacetyl, (2-napthoxy)acetyl, trans-cinnamoyl, picolinyl, 3-amino-4-hydroxybenzoyl, (4-pyridylthio)acetyl, 2,4-dichlorobenzoyl, 3,4-dichlorobenzoyl, 4-biphenylcarboxy, thiophenoxyacetyl, 1-benzoylpropionyl, phenylacetyl, hydrocinnamoyl, 3,3-diphenylpropionyl, 3,3,3-triphenylpropionyl, 4-phenylbutyryl, phenoxyacetyl, (+/-)-2-phenoxypropionyl, 2,4-dimethoxybenzoyl, 3,4-dimethoxybenzoyl, 3,4-dihydroxybenzoyl, 2,4-dihydroxybenzoyl, 3,4,5-trimethoxybenzoyl, 3,4,5-triethoxybenzoyl, 3,4,5-trihydroxybenzoyl, 2-benzoylbenzoyl, 1-napthoyl, xanthene-9-carboxy, 4-chloro-2-nitrobenzoyl, 2-chloro-4-nitrobenzoyl, 4-chloro-3-nitrobenzoyl, 2-chloro-5-nitrobenzoyl, 4-(dimethylamino)benzoyl, 4-(diethylamino)benzoyl, 4-nitrobenzoyl, 3-(dimethylamino)benzoyl, p-methylbenzoyl, p-methoxybenzoyl, trimethylacetyl, tert-butylacetyl, (-)-menthoxyacetyl, cyclohexanecarboxy, cyclohexylacetyl, dicyclohexylacetyl, 4-cyclohexylbutyroyl, cycloheptanecarboxy, 13-isopropylpodocarpa-7,13-dien-15-oyl, acetyl, octanoyl, (methylthio)acetyl, 3-nitropropionyl, 4-amino-3 hydroxybenzoyl, 3-(2-methyl-4-nitro-1-imidizoyl)propionyl, 2-furoyl, (s)(-)-2-pyrrolidone-5-carboxy, (2-pyrimidylthio)acetyl,

4-methoxy-2-quinolinecarboxy, 1-adamantanecarboxy, piperonoyl, 5-methyl-3-phenylisoxazole-4-carboxy, rhodanine-3-acetyl, 2-norbornaneacetyl, nicotinoyl, 9-oxo-9H-thioxanthene-3-carboxyl-10,10 dioxide, 2-thiophenecarboxy, 5-nitro-2-furanoyl, indole-3-acetyl, isonicotinoyl, 3α-hydroxy-5β-cholan-24-oyl, (3α,7α,12α)-trihydroxy-5β-cholan-24-oyl, (3α, 5β-12α)-3,12, dihydroxy-5-cholan-24-oyl, (3α, 5β, 6α)-3,6-dihydroxy-cholan-24-oyl, L-alaninyl, L-cysteinyl, L-aspartinyl, L-glutaminyl, L-phenylalaninyl, glycinyl, L-histidinyl, L-isoleucinyl, L-lyscinyl, L-leucinyl, L-methionylsulfoxide, L-methionyl, L-asparginyl, L-prolinyl, L-glutaminyl, L-arganinyl, L-serinyl, L-threoninyl, L-valinyl, L-tryptophanoyl, L-tyrosinyl, D-alaninyl, D-cysteinyl, D-aspartinyl, D-glutaminyl, D-phenylalaninyl, glycinyl, D-histidinyl, D-isoleucinyl, D-lyscinyl, D-leucinyl, D-methionylsulfoxide, D-methionyl, D-asparginyl, D-prolinyl, D-glutaminyl, D-arganinyl, D-serinyl, D-threoninyl, D-valinyl, D-tryptophanoyl, D-tyrosinyl, 2-aminobutyroyl, 4-aminobutyroyl, 2-aminoisobutyroyl, L-norleucinyl, D-norleucinyl, 6-aminohexanoyl, 7-aminoheptanoyl, thioprolinyl, L-norvalinyl, D-norvalinyl, α-ornithinyl, methionyl sulfonyl, L-naphthylalaninyl, D-naphthylalaninyl, L-phenylglycinyl, D-phenylglycinyl, ß-alaninyl, L-cyclohexylalaninyl, D-cyclohexylalaninyl, hydroxyprolinyl, 4-nitrophenylalaninyl, dehydroprolinyl, 3-hydroxy-1-propanesulfonyl, 1-propanesulfonyl, 1-octanesulfonyl, perfluoro-1-octanesulfonly, (+)-10-camphorsulfonyl, (-)-10-camphorsulfonyl, benzenesulfonyl, 2-nitrobenzenesulfonyl, p-toluenesulfonyl, 4-nitrobenzenesulfonyl, n-acetylsulfanilyl, 2,5-dichlorobenzenesulfonyl, 2,4-dinitrobenzenesulfonyl, 2-mesitylenesulfonyl or 2-napthalenesulfonyl;

n is 1; and

Y is $C(O)NH_2$ or C(O)NH bound to a functionalized resin.

In the above Formula I, the R^1-Y substituents are such that Y is always bonded to the 1-position of the R^1 radical. All naming above and hereinafter reflects this positioning between the two substituents.

In the above Formula I, the stereochemistry of chiral centers associated with the R^1 through R^8 groups can independently be in the R or S configuration, or a mixture of the two. These can be designated as R or S or R,S or d,D, l,L or d,l, D,L.

In the above Formula I, the term "C_1 to C_{10} alkyl" denotes such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, amyl, tert-amyl, hexyl and the like. The preferred "C_1 to C_{10} alkyl" group is methyl.

The term "C_2 to C_{10} alkenyl" denotes such radicals as vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, as well as dienes and trienes of straight and branched chains.

The term "C_2 to C_{10} alkynyl" denotes such radicals as ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, as well as di- and tri-ynes of straight and branched chains.

The term "C_1 to C_{10} alkylene" means a C_1 to C_{10} alkyl group where the alkyl radical is bonded at two positions connecting together two separate additional groups. Examples of C_1 to C_{10} alkylene include methylene, 1,2-ethyl, 1,1-ethyl, 1,3-propyl and the like. The term "C_2 to C_{10} alkenylene" means a C_2 to C_{10} alkenyl radican which is bonded at two positions connecting together two separate additional groups.

The terms "C_1 to C_{10} substituted alkyl," "C_2 to C_{10} substituted alkenyl," and "C_2 to C_{10} substituted alkynyl," denote that the above C_1 to C_{10} alkyl groups and C_2 to C_{10} alkenyl and alkynyl groups are substituted by one or more, and preferably one or two, halogen, hydroxy, protected hydroxy, oxo, protected oxo, cyclohexyl, naphthyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, imidazolyl, indolyl, pyrrolidinyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, nitro, C_1 to C_7 alkyl ester, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6_ alkyl)carboxamide, N,N-di(C_1 to C_6 alkyl)carboxamide, cyano, methylsulfonylamino, thio, C_1 to C_4 alkylthio or C_1 to C_4 alkyl sulfonyl groups. The substituted alkyl, alkenyl or alkynyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents.

Examples of the above substituted alkyl groups include the 2-oxo-prop-1-yl, 3-oxo-but-1-yl, cyanomethyl, nitromethyl, chloromethyl, hydroxymethyl, tetrahydropyranyloxymethyl, trityloxymethyl, propionyloxymethyl, amino, methylamino, aminomethyl, dimethylamino, carboxymethyl, allyloxycarbonylmethyl, allyloxycarbonylaminomethyl, methoxymethyl, ethoxymethyl, t-butoxymethyl, acetoxymethyl, chloromethyl,

bromomethyl, iodomethyl, trifluoromethyl, 6-hydroxyhexyl, 2,4-dichloro(n-butyl), 2-aminopropyl, chloroethyl, bromoethyl, fluoroethyl, iodoethyl, chloropropyl, bromopropyl, fluoropropyl, iodopropyl, 2-aminoethyl, 1-aminoethyl, N-benzoyl-2-aminoethyl, N-acetyl-2-aminoethyl, N-benzoyl-1-aminoethyl, N-acetyl-1-aminoethyl and the like.

Examples of the above substituted alkenyl groups include styrenyl, 3-chloro-propen-1-yl, 3-chloro-buten-1-yl, 3-methoxy-propen-2-yl, 3-phenyl-buten-2-yl, 1-cyano-buten-3-yl and the like. The geometrical isomerism is not critical, and all geometrical isomers for a given substituted alkenyl can be used.

Examples of the above substituted alkynyl groups include phenylacetylen-1-yl, 1-phenyl-2-propyn-1-yl and the like.

In preferred embodiments of the subject invention C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_2 to C_{10} alkynyl, C_1 to C_{10} substituted alkyl, C_2 to C_{10} substituted alkenyl, or C_2 to C_{10} substituted alkynyl are preferably C_1 to C_7 or C_2 to C_8, respectively, and more preferably, C_1 to C_6 and C_2 to C_7. However, it should be appreciated by those of skill in the art that one or a few carbons could be added to an alkyl, alkenyl, alkynyl, substituted or unsubstituted, without substantially modifying the structure and function of the subject compounds and that, therefore, such additions would not depart from the spirit of the invention.

The term "C_1 to C_{10} substituted alkylene" means a C_1 to C_{10} alkyl group where the alkyl radical is bonded at two positions connecting together two separate additional groups and further bearing an additional substituent. Examples of C_1 to C_{10} substituted alkylene include aminomethylene, 1-

(amino)-1,2-ethyl, 2-(amino)-1,2-ethyl, 1-(acetamido)-1,2-ethyl, 2-(acetamido)-1,2-ethyl, 2-hydroxy-1,1-ethyl, 1-(amino)-1,3-propyl. Similarly, the term "C_2 to C_{10} substituted alkenylene" means a C_2 to C_{10} substituted alkenyl group where the alkenyl radical is bonded at two positions connecting together two separate additional groups and further bearing an additional substituent.

The term "oxo" denotes a carbon atom bonded to two additional carbon atoms substituted with an oxygen atom doubly bonded to the carbon atom, thereby forming a ketone moiety.

The term "protected oxo" denotes a carbon atom bonded to two additional carbon atoms substituted with two alkoxy groups or twice bonded to a substituted diol moiety, thereby forming an acyclic or cyclic ketal moiety.

The term "C_1 to C_7 alkoxy" as used herein denotes groups such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy and like groups. A preferred alkoxy is methoxy. The term "C_1 to C_7 substituted alkoxy" means the alkyl portion of the alkoxy can be substituted in the same manner as in relation to C_1 to C_6 substituted alkyl.

The term "C_1 to C_7 acyloxy" denotes herein groups such as formyloxy, acetoxy, propionyloxy, butyryloxy, pentanoyloxy, hexanoyloxy, heptanoyloxy and the like.

Similarly, the term "C_1 to C_7 acyl" encompasses groups such as formyl, acetyl, propionyl, butyryl, pentanoyl, pivaloyl, hexanoyl, heptanoyl, benzoyl and the like. Preferred acyl groups are acetyl and benzoyl.

The term "C_1 to C_7 substituted acyl" denotes the acyl group substituted by one or more, and preferably one or two, halogen, hydroxy, protected hydroxy, oxo, protected oxo, cyclohexyl, naphthyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, imidazolyl, indolyl, pyrrolidinyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, nitro, C_1 to C_7 alkyl ester, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N,N-di(C_1 to C_6 alkyl)carboxamide, cyano, methylsulfonylamino, thio, C_1 to C_4 alkylthio or C_1 to C_4 alkyl sulfonyl groups. The substituted acyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents.

Examples of C_1 to C_7 substituted acyl include 4-phenylbutyroyl, 3-phenylbutyroyl, 3-phenylpropanoyl, 2-cyclohexanylacetyl, cyclohexanecarbonyl, 2-furanoyl and 3-(dimethylamino)benzoyl.

The substituent term "C_3 to C_7 cycloalkyl" includes the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl rings. The substituent term "C_3 to C_7 substituted cycloalkyl" indicates the above cycloalkyl rings substituted by one or two halogen, hydroxy, protected hydroxy, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, oxo, protected oxo, (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, protected carboxy, phenyl, substituted phenyl, amino, or protected amino groups.

The term "C_5 to C_7 cycloalkenyl" indicates a 1,2, or 3-cyclopentenyl ring, a 1,2,3 or 4-cyclohexenyl ring or a 1,2,3,4 or 5-cycloheptenyl ring, while the term "C_5 to C_7 substituted cycloalkenyl" denotes the above C_5 to C_7 cycloalkenyl rings substituted by a C_1 to C_6 alkyl radical,

halogen, hydroxy, protected hydroxy, C_1 to C_7 alkoxy, trifluoromethyl, carboxy, protected carboxy, oxo, protected oxo, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, phenyl, substituted phenyl, amino, or protected amino.

The term "heterocyclic ring" denotes optionally substituted five-membered or six-membered rings that have 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms. These five-membered or six-membered rings may be saturated, fully saturated or partially unsaturated, with fully saturated rings being preferred. A "substituted heterocyclic ring" means any of the above-described heterocycles substituted with any of the substituents as referred to above in relation to substituted phenyl. An "amino-substituted heterocyclic ring" means any one of the above-described heterocyclic rings is substituted with at least one amino group. Preferred heterocyclic rings include morpholino, piperidinyl, piperazinyl, tetrahydrofurano, pyrrolo, and tetrahydrothiophen-yl.

The abbreviation "Ar" stands for an aryl group. Aryl groups which can be used with present invention include phenyl, substituted phenyl, as defined above, heteroaryl, and substituted heteroaryl. The term "heteroaryl" or "heteroaryl ring" means a heterocyclic aromatic derivative which is a five-membered or six-membered ring system having from 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms. Examples of heteroaryls include pyridinyl, pyrimidinyl, and pyrazinyl, pyridazinyl, pyrrolo, furano, oxazolo, isoxazolo, thiazolo and the like.

The term "substituted heteroaryl" or "substituted heteroaryl ring" means the above-described heteroaryl is substituted with, for example, one or more, and preferably one or two, substituents which are the same or different which substituents can be halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino or N-(phenylsulfonyl)amino groups.

The term "C_7 to C_{12} phenylalkyl" denotes a C_1 to C_6 alkyl group substituted at any position by a phenyl ring. Examples of such a group include benzyl, 2-phenylethyl, 3-phenyl(n-propyl), 4-phenylhexyl, 3-phenyl(n-amyl), 3-phenyl(sec-butyl) and the like. Preferred C_7 to C_{12} phenylalkyl groups are the benzyl and the phenylethyl groups.

The term "C_7 to C_{12} substituted phenylalkyl" denotes a C_7 to C_{12} phenylalkyl group substituted on the C_1 to C_6 alkyl portion with one or more, and preferably one or two, groups chosen from halogen, hydroxy, protected hydroxy, oxo, protected oxo, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-C_1 to C_6 alkyl)carboxamide, N, N-(C_1 to C_6 dialkyl)carboxamide, cyano, N-((C_1 to C_6

alkylsulfonyl)amino, thiol, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfonyl groups; and/or the phenyl group may be substituted with one or more, and preferably one or two, substituents chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl) carboxamide, protected N-(C_1 to C_6 alkyl) carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino, cyclic C_2 to C_7 alkylene or a phenyl group, substituted or unsubstituted, for a resulting biphenyl group. The substituted alkyl or phenyl groups may be substituted with one or more, and preferably one or two, substituents which can be the same or different.

Examples of the term "C_7 to C_{12} substituted phenylalkyl" include groups such as 2-phenyl-1-chloroethyl, 2-(4-methoxyphenyl)ethyl, 4-(2,6-dihydroxy phenyl)n-hexyl, 2-(5-cyano-3-methoxyphenyl)n-pentyl, 3-(2,6-dimethylphenyl)n-propyl, 4-chloro-3-aminobenzyl, 6-(4-methoxyphenyl)-3-carboxy(n-hexyl), 5-(4-aminomethylphenyl)-3-(aminomethyl)n-pentyl, 5-phenyl-3-oxo-n-pent-1-yl and the like.

The term "substituted phenyl" specifies a phenyl group substituted with one or more, and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino,

(disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or phenyl, substituted or unsubstituted, such that, for example, a biphenyl results.

Examples of the term "substituted phenyl" include a mono- or di(halo)phenyl group such as 2, 3 or 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2, 3 or 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2, 3 or 4-fluorophenyl and the like; a mono or di(hydroxy)phenyl group such as 2, 3 or 4-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 2, 3 or 4-nitrophenyl; a cyanophenyl group, for example, 2, 3 or 4-cyanophenyl; a mono- or di(alkyl)phenyl group such as 2, 3 or 4-methylphenyl, 2,4-dimethylphenyl, 2, 3 or 4-(iso-propyl)phenyl, 2, 3 or 4-ethylphenyl, 2, 3 or 4-(n-propyl)phenyl and the like; a mono or di(alkoxyl)phenyl group, for example, 2,6-dimethoxyphenyl, 2, 3 or 4-methoxyphenyl, 2, 3 or 4-ethoxyphenyl, 2, 3 or 4-(isopropoxy)phenyl, 2, 3 or 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 2, 3 or 4-trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such as 2, 3 or 4-carboxyphenyl or 2,4-di(protected carboxy)phenyl; a mono-or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 2, 3, or 4-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2, 3 or 4-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 2, 3 or 4-(N-(methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups wherein the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-

methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy 4-chlorophenyl and the like.

The term "phenylene" means a phenyl group where the phenyl radical is bonded at two positions connecting together two separate additional groups. Examples of phenylene include 1,2-phenyl, 1,3-phenyl, and 1,4-phenyl.

The term "substituted phenylene" means a substituted phenyl group where the phenyl radical is bonded at two positions connecting together two separate additional groups. Examples of substituted phenylene include 3-chloro-1,2-phenyl, 4-amino-1,3-phenyl, and 3-hydroxy-1,4-phenyl.

The term "phenoxy" denotes a phenyl bonded to an oxygen atom provided that the phenoxy is bonded to the quinoline ring through the oxygen atom as opposed to a carbon atom of the phenyl ring. The term "substituted phenoxy" specifies a phenoxy group substituted with one or more, and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino and N-(phenylsulfonyl)amino.

Examples of substituted phenoxy include 2-methylphenoxy, 2-ethylphenoxy, 2-propylphenoxy, 2-isopropylphenoxy, 2-sec-butylphenoxy, 2-

tert-butylphenoxy, 2-allylphenoxy, 2-propenylphenoxy, 2-cyclopentylphenoxy, 2-fluorophenoxy, 2-(trifluoromethyl)phenoxy, 2-chlorophenoxy, 2-bromophenoxy, 2-methoxyphenoxy, 2-ethoxyphenoxy, 2-isopropoxyphenoxy, 3-methylphenoxy, 3-ethylphenoxy, 3-isopropylphenoxy, 3-tert-butylphenoxy, 3-pentadecylphenoxy, 3-(trifluoromethyl)phenoxy, 3-fluorophenoxy, 3-chlorophenoxy, 3-bromophenoxy, 3-iodophenoxy, 3-methoxyphenoxy, 3-(trifluoromethoxy)phenoxy, 4-methylphenoxy, 4-ethylphenoxy, 4-propylphenoxy, 4-isopropylphenoxy, 4-sec-butylphenoxy, 4-tert-butylphenoxy, 4-tert-amylphenoxy, 4-nonylphenoxy, 4-dodecylphenoxy, 4-cyclopenylphenoxy, 4-(trifluoromethyl)phenoxy, 4-fluorophenoxy, 4-chlorophenoxy, 4-bromophenoxy4-iodophenoxy, 4-methoxyphenoxy, 4-(trifluoromethoxy)phenoxy, 4-ethoxyphenoxy, 4-propoxyphenoxy, 4-butoxyphenoxy, 4-hexyloxyphenoxy, 4-heptyloxyphenoxy, 2,3-dimethylphenoxy, 5,6,7,8-tetrahydro-1-naphthoxy, 2,3-dichlorophenoxy, 2,3-dihydro-2,2-dimethyl-7-benzofuranoxy, 2,3-dimethoxyphenoxy, 2,6-dimethylphenoxy, 2,6-diisopropylphenoxy, 2,6-di-sec-butylphenoxy, 2-tert-butyl-6-methylphenoxy, 2,6-di-tert-butylphenoxy, 2-allyl-6-methylphenoxy, 2,6-difluorophenoxy, 2,3-difluorophenoxy, 2,6-dichlorophenoxy, 2,6-dibromophenoxy, 2-fluoro-6-methoxyphenoxy, 2,6-dimethoxyphenoxy, 3,5-dimethylphenoxy, 5-isopropyl-3-methylphenoxy, 3,5-di-tert-butylphenoxy, 3,5-bis(trifluoromethyl)phenoxy, 3,5-difluorophenoxy, 3,5-dichlorophenoxy, 3,5-dimethoxyphenoxy, 3-chloro-5-methoxyphenoxy, 3,4-dimethylphenoxy, 5-indanoxy, 5,6,7,8-tetrahydro-2-naphthoxy, 4-chloro-3-methylphenoxy, 2,4-dimethylphenoxy, 2,5-dimethylphenoxy, 2-isopropyl-5-methylphenoxy, 4-isopropyl-3-methylphenoxy, 5-isopropyl-2-methylphenoxy, 2-tert-butyl-5-methylphenoxy, 2-tert-butyl-4-methylphenoxy, 2,4-di-tert-butylphenoxy, 2,4-di-tert-amylphenoxy, 4-fluoro-2-methylphenoxy, 4-fluoro-3-methylphenoxy, 2-chloro-4-methylphenoxy, 2-chloro-5-methylphenoxy, 4-chloro-2-methylphenoxy, 4-chloro-3-ethylphenoxy, 2-bromo-4-methylphenoxy, 4-iodo-

2-methylphenoxy, 2-chloro-5-(trifluoromethyl)phenoxy, 2,4-difluorophenoxy, 2,5-difluorophenoxy, 3,4-difluorophenoxy, 4-chloro-2-fluorophenoxy, 3-chloro-4-fluorophenoxy, 4-chloro-3-fluorophenoxy, 2-bromo-4-fluorophenoxy, 4-bromo-2-fluorophenoxy, 2-bromo-5-fluorophenoxy, 2,4-dichlorophenoxy, 3,4-dichlorophenoxy, 2,5-dichlorophenoxy, 2-bromo-4-chlorophenoxy, 2-chloro-4-fluorophenoxy, 4-bromo-2-chlorophenoxy, 2,4-dibromophenoxy, 2-methoxy-4-methylphenoxy, 4-allyl-2-methylphenoxy, trans-2-ethoxy-5-(1-propenyl)phenoxy, 2-methoxy-4-propenylphenoxy, 3,4-dimethoxyphenoxy, 3-ethoxy-4-methoxyphenoxy, 4-allyl-2,6-dimethoxyphenoxy, 3,4-methylenedioxyphenoxy, 2,3,6-trimethylphenoxy, 2,4-dichloro-3-methylphenoxy, 2,3,4-trifluorophenoxy, 2,3,6-trifluorophenoxy, 2,3,5-trifluorophenoxy, 2,3,4-trichlorophenoxy, 2,3,6-trichlorophenoxy, 2,3,5-trimethylphenoxy, 3,4,5-trimethylphenoxy, 4-chloro-3,5-dimethylphenoxy, 4-bromo-3,5-dimethylphenoxy, 2,4,6-trimethylphenoxy, 2,6-bis(hydroxymethyl)-4-methylphenoxy, 2,6-di-tert-butyl-4-methylphenoxy, 2,6-di-tert-butyl-4-methoxyphenoxy, 2,4,5-trifluorophenoxy, 2-chloro-3,5-difluorophenoxy, 2,4,6-trichlorophenoxy, 3,4,5-trimethoxyphenoxy, 2,3,5-trichlorophenoxy, 4-bromo-2,6-dimethylphenoxy, 4-bromo-6-chloro-2-methylphenoxy, 2,6-dibromo-4-methylphenoxy, 2,6-dichloro-4-fluorophenoxy, 2,6-dibromo-4-fluorophenoxy, 2,4,6-tribromophenoxy, 2,4,6-triiodophenoxy, 2-chloro-4,5-dimethylphenoxy, 4-chloro-2-isopropyl-5-methylphenoxy, 2-bromo-4,5-difluorophenoxy, 2,4,5-trichlorophenoxy, 2,3,5,6-tetrafluorophenoxy and the like.

The term "C_7 to C_{12} phenylalkoxy" denotes a C_7 to C_{12} phenylalkoxy group, provided that the phenylalkoxy is bonded to the quinoline ring through the oxygen atom. By "C_7 to C_{12} substituted phenylalkoxy" is meant C_7 to C_{12} phenylalkoxy group which can be substituted on the C_1 to C_6 alkyl portion with one or more, and preferably one or two, groups chosen from halogen, hydroxy, protected hydroxy, oxo, protected oxo, amino, protected

amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-C_1 to C_6 alkyl)carboxamide, N, N-(C_1 to C_6 dialkyl)carboxamide, cyano, N-((C_1 to C_6 alkylsulfonyl)amino, thiol, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfonyl groups; and/or the phenyl group can be substituted with one or more, and preferably one or two, substituents chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl) carboxamide, protected N-(C_1 to C_6 alkyl) carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or a phenyl group, substituted or unsubstituted, for a resulting biphenyl group. The substituted alkyl or phenyl groups may be substituted with one or more, and preferably one or two, substituents which can be the same or different.

Examples of the term "C_7 to C_{12} substituted phenylalkoxy" include groups such as 2-(4-hydroxyphenyl)ethoxy, 4-(4-methoxyphenyl)butoxy, (2R)-3-phenyl-2-amino-propoxy, (2S)-3-phenyl-2-amino-propoxy, 2-indanoxy, 6-phenyl-1-hexanoxy, cinnamyloxy, (+/-)-2-phenyl-1-propoxy, 2,2-dimethyl-3-phenyl-1-propoxy and the like.

The term "phthalimide" means a cyclic imide which is made from phthalic acid, also called 1, 2 benezene-dicarboxylic acid. The term "substituted phthalimide" specifies a phthalimide group substituted with one or more, and

preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino and N-(phenylsulfonyl)amino.

Examples of substituted phthalimides include 4,5-dichlorophthalimido, 3-fluorophthalimido, 4-methoxyphthalimido, 3-methylphthalimido, 4-carboxyphthalimido and the like.

The term "substituted naphthyl" specifies a naphthyl group substituted with one or more, and preferably one or two, moieties either on the same ring or on different rings chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_6 alkyl)carboxamide, protected N-(C_1 to C_6 alkyl)carboxamide, N, N-di(C_1 to C_6 alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_6 alkyl)sulfonyl)amino or N-(phenylsulfonyl)amino.

Examples of substituted naphthyl include a mono or di(halo)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-chloronaphthyl, 2, 6-dichloronaphthyl, 2, 5-dichloronaphthyl, 3, 4-dichloronaphthyl, 1, 2, 3, 4, 5, 6,

7 or 8-bromonaphthyl, 3, 4-dibromonaphthyl, 3-chloro-4-fluoronaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-fluoronaphthyl and the like; a mono or di(hydroxy)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-hydroxynaphthyl, 2, 4-dihydroxynaphthyl, the protected-hydroxy derivatives thereof and the like; a nitronaphthyl group such as 3- or 4-nitronaphthyl; a cyanonaphthyl group, for example, 1, 2, 3, 4, 5, 6, 7 or 8-cyanonaphthyl; a mono- or di(alkyl)naphthyl group such as 2, 3, 4, 5, 6, 7 or 8-methylnaphthyl, 1, 2, 4-dimethylnaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(isopropyl)naphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-ethylnaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(n-propyl)naphthyl and the like; a mono or di(alkoxy)naphthyl group, for example, 2, 6-dimethoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8- methoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-ethoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(isopropoxy)naphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(t-butoxy)naphthyl, 3-ethoxy-4-methoxynaphthyl and the like; 1, 2, 3, 4, 5, 6, 7 or 8-trifluoromethylnaphthyl; a mono- or dicarboxynaphthyl or (protected carboxy)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-carboxynaphthyl or 2, 4-di(-protected carboxy)naphthyl; a mono-or di(hydroxymethyl)naphthyl or (protected hydroxymethyl)naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(protected hydroxymethyl)naphthyl or 3, 4-di(hydroxymethyl)naphthyl; a mono- or di(amino)naphthyl or (protected amino)naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(amino)naphthyl or 2, 4-(protected amino)-naphthyl, a mono- or di(aminomethyl)naphthyl or (protected aminomethyl)naphthyl such as 2, 3, or 4-(aminomethyl)naphthyl or 2, 4-(protected aminomethyl)-naphthyl; or a mono- or di-(N-methylsulfonylamino) naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(N-methylsulfonylamino)naphthyl. Also, the term "substituted naphthyl" represents disubstituted naphthyl groups wherein the substituents are different, for example, 3-methyl-4-hydroxynaphth-1-yl, 3-chloro-4-hydroxynaphth-2-yl, 2-methoxy-4-bromonaphth-1-yl, 4-ethyl-2-hydroxynaphth-1-yl, 3-hydroxy-4-nitronaphth-2-yl, 2-hydroxy-4-chloronaphth-1-yl, 2-methoxy-7-bromonaphth-1-yl, 4-ethyl-5-hydroxynaphth-2-yl, 3-hydroxy-8-nitronaphth-2-yl, 2-hydroxy-5-chloronaphth-1-yl and the like.

The terms "halo" and "halogen" refer to the fluoro, chloro, bromo or iodo groups. There can be one or more halogen, which are the same or different. Preferred halogens are chloro and fluoro.

The term "(monosubstituted)amino" refers to an amino group with one substituent chosen from the group consisting of phenyl, substituted phenyl, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 acyl, C_2 to C_7 alkenyl, C_2 to C_7 substituted alkenyl, C_2 to C_7 alkynyl, C_2 to C_7 substituted alkynyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl and heterocyclic ring. The (monosubstituted)amino can additionally have an amino-protecting group as encompassed by the term "protected (monosubstituted)amino."

The term "(disubstituted)amino" refers to amino groups with two substituents chosen from the group consisting of phenyl, substituted phenyl, C_1 to C_6 alkyl, C_1 to C_6 substituted alkyl, C_1 to C_7 acyl, C_2 to C_7 alkenyl, C_2 to C_7 alkynyl, C_7 to C_{12} phenylalkyl, and C_7 to C_{12} substituted phenylalkyl. The two substituents can be the same or different.

The term "amino-protecting group" as used herein refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups of the molecule. The term "protected (monosubstituted)amino" means there is an amino-protecting group on the monosubstituted amino nitrogen atom. In addition, the term "protected carboxamide" means there is an amino-protecting group on the carboxamide nitrogen.

Examples of such amino-protecting groups include the formyl ("For") group, the trityl group, the phthalimido group, the trichloroacetyl group,

the chloroacetyl, bromoacetyl, and iodoacetyl groups, urethane-type blocking groups, such as t-butoxycarbonyl ("Boc"), 2-(4-biphenylyl)propyl-2-oxycarbonyl ("Bpoc"), 2-phenylpropyl-2-oxycarbonyl ("Poc"), 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenylethyl-1-oxycarbonyl, 1,1-diphenylpropyl-1-oxycarbonyl, 2-(3,5-dimethoxyphenyl)propyl-2-oxycarbonyl ("Ddz"), 2-(p-toluyl)propyl-2-oxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxy-carbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)-ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, 9-fluorenylmethoxycarbonyl ("Fmoc"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyl-oxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl, benzyloxycarbonyl ("Cbz"), 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxy-carbonyl, α-2,4,5,-tetramethylbenzyloxycarbonyl ("Tmz"), 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyl-oxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxy-carbonyl, 4-cyanobenzyloxycarbonyl, 4-(decyloxy)benzyloxycarbonyl and the like; the benzoylmethylsulfonyl group, dithiasuccinoyl ("Dts"), the 2-(nitro)phenylsulfenyl group ("Nps"), the diphenyl-phosphine oxide group and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the conditions of the subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the compounds. Preferred amino-protecting groups are Boc, Cbz and Fmoc. Further examples of amino-protecting groups embraced by the above term are well known in organic

synthesis and the peptide art and are described by, for example, T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 7, M. Bodanzsky, "Principles of Peptide Synthesis," 1st and 2nd revised ed., Springer-Verlag, New York, NY, 1984 and 1993, and Stewart and Young, "Solid Phase Peptide Synthesis," 2nd ed., Pierce Chemical Co., Rockford, IL, 1984, each of which is incorporated herein by reference. The related term "protected amino" defines an amino group substituted with an amino-protecting group discussed above.

The term "carboxy-protecting group" as used herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid protecting groups include t-butyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, 2-phenylpropyl, trimethylsilyl, t-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, β-(trimethylsilyl)ethyl, β-(di(n-butyl)methylsilyl)ethyl, p-toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)propenyl and like moieties. The species of carboxy-protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the conditions of subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. Further examples of these groups are found in E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 5, each of which is incorporated herein by reference. A related term is "protected carboxy," which

refers to a carboxy group substituted with one of the above carboxy-protecting groups.

The term "hydroxy-protecting group" refers to readily cleavable groups bonded to hydroxyl groups, such as the tetrahydropyranyl, 2-methoxypropyl, 1-ethoxyethyl, methoxymethyl, 2-methoxyethoxymethyl, methylthiomethyl, t-butyl, t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, benzyl, allyl, trimethylsilyl, (t-butyl)dimethylsilyl, 2,2,2-trichloroethoxycarbonyl groups and the like. The species of hydroxy-protecting group is not critical so long as the derivatized hydroxyl group is stable to the conditions of subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. Further examples of hydroxy-protecting groups are described by C.B. Reese and E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapters 3 and 4, respectively, and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapters 2 and 3. Related terms are "protected hydroxy," and "protected hydoxymethyl" which refer to a hydroxy or hydroxymethyl substituted with one of the above hydroxy-protecting groups.

The substituent term "C_1 to C_4 alkylthio" refers to sulfide groups such as methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, t-butylthio and like groups.

The substituent term "C_1 to C_4 alkylsulfoxide" indicates sulfoxide groups such as methylsulfoxide, ethylsulfoxide, n-propylsulfoxide, isopropylsulfoxide, n-butylsulfoxide, sec-butylsulfoxide and the like.

The term "C_1 to C_4 alkylsulfonyl" encompasses groups such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, t-butylsulfonyl and the like.

The terms "C_1 to C_4 substituted alkylthio," "C_1 to C_4 substituted alkylsulfoxide," and "C_1 to C_4 substituted alkylsulfonyl," denote the C_1 to C_4 alkyl portion of these groups may be substituted as described above in relation to "substituted alkyl."

The terms "phenylthio,"phenylsulfoxide," and "phenylsulfonyl" specify a thiol, a sulfoxide, or sulfone, respectively, containing a phenyl group. The terms "substituted phenylthio," "substituted phenylsulfoxide," and "substituted phenylsulfonyl" mean that the phenyl of these groups can be substituted as described above in relation to "substituted phenyl."

The term "C_1 to C_6 alkylaminocarbonyl" means a C_1 to C_6 alkyl attached to an aminocarbonyl group, where the C_1 to C_6 alkylaminocarbonyl groups are the resulting urea when an isocyanate is used in the reaction scheme. Examples of C_1 to C_6 alkylaminocarbonyl include methylaminocarbonyl (from methylisocyanate), ethylaminocarbonyl (from ethylisocyanate), propylaminocarbonyl (from propylisocyanate), butylaminocarbonyl (from butylisocyatate). The term "C_1 to C_6 substituted alkylaminocarbonyl" denotes a substituted alkyl bonded to an aminocarbonyl group, which alkyl may be substituted as described above in relation to C_1 to C_6 substituted alkyl. Examples of C_1 to C_6 substituted alkylaminocarbonyl include, for example, methoxymethylaminocarbonyl (from methoxymethylisocyanate), 2-chloroethylaminocarbonyl (from 2-chloroethylisocyanate), 2-oxopropylaminocarbonyl (from 2-oxopropylisocyanate), and 4-phenylbutylaminocarbonyl (from phenylbutylisocyanate).

The term "phenylaminocarbonyl" means a phenyl attached to an aminocarbonyl group, where the phenylaminocarbonyl groups are the result of using a phenylisocyanate in the reaction scheme. The term "substituted phenylaminocarbonyl" denotes a substituted phenyl bonded to an aminocarbonyl group, which phenyl may be substituted as described above in relation to substituted phenyl. Examples of substituted phenylaminocarbonyl include 2-chlorophenylaminocarbonyl (from 2-chlorophenylisocyanate), 3-chlorophenylaminocarbonyl (from 3-chlorophenylisocyanate), 2-nitorphenylaminocarbonyl (from 2-nitrophenylisocyanate), 4-biphenylaminocarbonyl (from 4-biphenylisocyanate), and 4-methoxyphenylaminocarbonyl (from 4-methoxyphenylisocyanate).

The substituent terms "cyclic C_2 to C_7 alkylene," "substituted cyclic C_2 to C_7 alkylene," "cyclic C_2 to C_7 heteroalkylene," and "substituted cyclic C_2 to C_7 heteroalkylene," define such a cyclic group bonded ("fused") to the phenyl radical resulting in a bicyclic ring system. The cyclic group may be saturated or contain one or two double bonds. Furthermore, the cyclic group may have one or two methylene or methine groups replaced by one or two oxygen, nitrogen or sulfur atoms which are the cyclic C_2 to C_7 heteroalkylene.

The cyclic alkylene or heteroalkylene group may be substituted once or twice by the same or different substituents selected from the group consisting of the following moieties: hydroxy, protected hydroxy, carboxy, protected carboxy, oxo, protected oxo, C_1 to C_4 acyloxy, formyl, C_1 to C_7 acyl, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfoxide, C_1 to C_4 alkylsulfonyl, halo, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, hydroxymethyl and a protected hydroxymethyl.

The cyclic alkylene or heteroalkylene group fused onto the benzene radical can contain two to ten ring members, but it preferably contains three to six members. Examples of such saturated cyclic groups are when the resultant bicyclic ring system is 2,3-dihydro-indanyl and a tetralin ring. When the cyclic groups are unsaturated, examples occur when the resultant bicyclic ring system is a naphthyl ring or indolyl. Examples of fused cyclic groups which each contain one nitrogen atom and one or more double bond, preferably one or two double bonds, are when the phenyl is fused to a pyridino, pyrano, pyrrolo, pyridinyl, dihydropyrrolo, or dihydropyridinyl ring. Examples of fused cyclic groups which each contain one oxygen atom and one or two double bonds are when the phenyl ring is fused to a furo, pyrano, dihydrofurano, or dihydropyrano ring. Examples of fused cyclic groups which each have one sulfur atom and contain one or two double bonds are when the phenyl is fused to a thieno, thiopyrano, dihydrothieno or dihydrothiopyrano ring. Examples of cyclic groups which contain two heteroatoms selected from sulfur and nitrogen and one or two double bonds are when the phenyl ring is fused to a thiazolo, isothiazolo, dihydrothiazolo or dihydroisothiazolo ring. Examples of cyclic groups which contain two heteroatoms selected from oxygen and nitrogen and one or two double bonds are when the benzene ring is fused to an oxazolo, isoxazolo, dihydrooxazolo or dihydroisoxazolo ring. Examples of cyclic groups which contain two nitrogen heteroatoms and one or two double bonds occur when the benzene ring is fused to a pyrazolo, imidazolo, dihydropyrazolo or dihydroimidazolo ring or pyrazinyl.

One or more of the tricyclic tetrahydroquinoline derivatives, even within a given library, may be present as a salt. The term "salt" encompasses those salts that form with the carboxylate anions and amine nitrogens and include salts formed with the organic and inorganic anions and cations discussed below. Furthermore, the term includes salts that form by standard

acid-base reactions with basic groups (such as amino groups) and organic or inorganic acids. Such acids include hydrochloric, sulfuric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, D-glutamic, D-camphoric, glutaric, phthalic, tartaric, lauric, stearic, salicyclic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic, and like acids.

The term "organic or inorganic cation" refers to counterions for the carboxylate anion of a carboxylate salt. The counter-ions are chosen from the alkali and alkaline earth metals, (such as lithium, sodium, potassium, barium, aluminum and calcium); ammonium and mono-, di- and tri-alkyl amines such as trimethylamine, cyclohexylamine; and the organic cations, such as dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl)ammonium, phenylethylbenzylammonium, dibenzylethylenediammonium, and like cations. See, for example, "Pharmaceutical Salts," Berge et al., J. Pharm. Sci., 66:1-19 (1977), which is incorporated herein by reference. Other cations encompassed by the above term include the protonated form of procaine, quinine and N-methylglucosamine, and the protonated forms of basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine and arginine. Furthermore, any zwitterionic form of the instant compounds formed by a carboxylic acid and an amino group is referred to by this term. For example, a cation for a carboxylate anion will exist when R_2 or R_3 is substituted with a (quaternary ammonium)methyl group. A preferred cation for the carboxylate anion is the sodium cation.

The compounds of the above Formulae can also exist as solvates and hydrates. Thus, these compounds may crystallize with, for example, waters of hydration, or one, a number of, or any fraction thereof of molecules of the

mother liquor solvent. The solvates and hydrates of such compounds are included within the scope of this invention.

One or more tricyclic tetrahydroquinoline derivatives, even when in a library, can be in the biologically active ester form, such as the non-toxic, metabolically-labile ester-form. Such ester forms induce increased blood levels and prolong the efficacy of the corresponding non-esterified forms of the compounds. Ester groups which can be used include the lower alkoxymethyl groups, for example, methoxymethyl, ethoxymethyl, isopropoxymethyl and the like; the α-(C_1 to C_7) alkoxyethyl groups, for example methoxyethyl, ethoxyethyl, propoxyethyl, isopropoxyethyl and the like; the 2-oxo-1,3-diooxlen-4-ylmethyl groups, such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, 5-phenyl-2-oxo-1,3-dioxolen-4-ylmethyl and the like; the C_1 to C_4 alkylthiomethyl groups, for example methylthiomethyl, ethylthiomethyl, iso-propylthiomethyl and the like; the acyloxymethyl groups, for example pivaloyloxymethyl, pivaloyloxyethyl, α-acetoxymethyl and the like; the ethoxycarbonyl-1-methyl group; the α-acetoxyethyl; the 1-(C_1 to C_7 alkyloxycarbonyloxy)ethyl groups such as the 1-(ethoxycarbonyloxy)ethyl group; and the 1-(C_1 to C_7 alkylaminocarbonyloxy)ethyl groups such as the 1-(methylaminocarbonyloxy)ethyl group.

The term "amino acid" includes any one of the twenty naturally-occurring amino acids or the D-form of any one of the naturally-occurring amino acids. In addition, the term "amino acid" also includes other non-naturally occurring amino acids besides the D-amino acids, which are functional equivalents of the naturally-occurring amino acids. Such non-naturally-occurring amino acids include, for example, norleucine ("Nle"), norvaline ("Nva"), β-Alanine, L- or D-naphthalanine, ornithine ("Orn"), homoarginine (homoArg) and others well known in the peptide art, such as

those described in M. Bodanzsky, "Principles of Peptide Synthesis," 1st and 2nd revised ed., Springer-Verlag, New York, NY, 1984 and 1993, and Stewart and Young, "Solid Phase Peptide Synthesis," 2nd ed., Pierce Chemical Co., Rockford, IL, 1984, both of which are incorporated herein by reference. Amino acids and amino acid analogs can be purchased commercially (Sigma Chemical Co.; Advanced Chemtech) or synthesized using methods known in the art.

The amino acids are indicated herein by either their full name or by the commonly known three letter code. Further, in the naming of amino acids, "D-" or "d-" designates an amino acid having the "D" configuration, as opposed to the naturally occurring L-amino acids. Where no specific configuration is indicated, one skilled in the art would understand the amino acid to be an L-amino acid. The amino acids can, however, also be in racemic mixtures of the D- and L-configuration or the D-amino acid can readily be substituted for that in the L-configuration.

As used herein, a chemical or combinatorial "library" is an intentionally created collection of differing molecules which can be prepared by the synthetic means provided below or otherwise and screened for biological activity in a variety of formats (e.g., libraries of soluble molecules, libraries of compounds attached to resin beads, silica chips or other solid supports). The libraries can be screened in any variety of assays, such as those detailed below as well as others useful for assessing the biological activity. The libraries are useful in their ability to rapidly synthesize and screen a diverse number or compounds. Moreover, the libraries will generally have at least one active compound and are generally prepared in such that the compounds are in equimolar quantities.

"Combinatorial chemistry" or "combinatorial synthesis" refers to the parallel synthesis of diverse compounds by sequential addition of reagents which leads to the generation of large chemical libraries having molecular diversity. Combinatorial chemistry, therefore, involves the systematic and repetitive, covalent connection of a set of different "building blocks" of varying structures to yield large arrays of diverse molecular entities.

The compounds of Formula I and combinatorial libraries containing the same can be prepared as set forth in the Reaction Schemes provided in the Figures and described below. The substituents R^1 to R^8 in the Reaction Schemes have the same meaning as those described above. The substituent Y in the Reaction Schemes is the same as defined above with the exception that it is still bound to resin or is the functionalized resin and, therefore, has one less hydrogen.

In brief, the tricyclic tetrahydroquinoline compounds of the present invention can be prepared according to Reaction Scheme I as shown in Figure 1. As depicted in Figure 1, a solid support resin-bound aniline (resin identified by a shaded circle) is reacted, in situ, with an aldehyde and is thereby, converted to the corresponding imine. This is performed in the presence of a dieneophile and an acid. In the presence of the dieneophile, the imine undergoes a hetero-Diels-Alder reaction and yields the tetrahydroquinoline.

More specifically, as shown by Reaction Scheme II in Figure 2, and as provided in Example 1, the tricyclic tetrahydroquinolines and libraries containing the same are prepared by the following more detailed steps. First, the anilines, (as shown in Figure 2), are coupled to resin, such as MBHA (Figure 2), MBA, Tentagel™ and the like as described below, using a carbodiimide coupling agent, such as dicyclohexylcarbodiimide, diisopropyl-

carbodiimide, N-dimethylaminoethyl-N'-ethyl-carbodiimide and the like, and an activator, such as 1-hydroxybenzotriazole, 7-aza-1-hydroxybenzotriazole and the like, in an aprotic polar solvent such as dichloromethane, dimethylformamide and the like, at between 10°C and 100°C, preferably at 25°C, for 2 to 24 hours, preferably 8 to 16 hours. The amino protecting group ("PG"), where necessary and used, is removed following standard procedures and the free amino group of the individual or mixtures of resin-bound anilines is condensed with an aldehyde in the presence of a dieneophile, such as cyclopentadiene, cyclohexadiene and the like and in the presence of an acid, such as trifluoroacetic acid, toluenesulfonic acid and the like, using in a polar solvent, such as dichloromethane, dimethylformamide, dimethylacetamide, N-methylpyrrolidinone or the like, for a period of 1 to 72 hours, usually 12 to 24 hours at 20°C to 75°C and preferably at 25°C to arrive at novel tricyclic tetrahydroquinoline derivatives. Where the dieneophile is regiochemically stable, such as cycloheadiene, it would be appreciated by those of skill in the art that it can be substituted without departing from the spirit of the invention. Such regiochemically stable dieneophiles can be substituted with, for example, C_1 to C10 alkyl, C_1 to C_7 alkoxy, or C_1 to C_7 acyloxy. Finally, the compounds can be cleaved from the resin by the methods common to those skilled in the art and the compounds tested for biological activity.

More specifically, as shown by Reaction Scheme III in Figure 3, the branched tricyclic tetrahydroquinolines and libraries containing the same are prepared by the following more detailed steps. First, as shown in Figure 3, N-Boc-nitrophenylalanines or, alternatively, the FMOC protected analogs are coupled to resin, such as MBHA, MBA, Tentagel™ and the like as described below, using a carbodiimide coupling agent, such as dicyclohexylcarbodiimide, diisopropyl-carbodiimide,N-dimethylaminoethyl-N'-ethyl-carbodiimide and the like, and an activator, such as 1-hydroxybenzotriazole,

7-aza-1-hydroxybenzotriazole and the like, in an aprotic polar solvent such as dichloromethane, dimethylformamide and the like, at between 10°C and 100°C, preferably at 25°C, for 2 to 24 hours, preferably 8 to 16 hours. The BOC of the α-amino group is removed using a strong acid such as trifluoroacetic acid or trifluoromethanesulfonic acid and the like (1-95%) in an aprotic solvent such as dichloromethane, dimethylformamide and the like, at between 10°C and 100°C, preferably at 25°C, for 2 to 24 hours, preferably 8 to 16 hours. Alternatively, the FMOC of the α amino acid is removed using an amine base such as piperidine, pyrrolidine, or morpholine and the like (1-95%) in an aprotic solvent such as dichloromethane, dimethylformamide and the like, at between 10°C and 100°C, preferably at 25°C, for 2 to 24 hours, preferably 8 to 16 hours. The free amino group is coupled to a carboxylic acid, such as acetic acid, benzoic acid and the like (Figure 3), using a carbodiimide coupling agent, such as dicyclohexylcarbodiimide, diisopropyl-carbodiimide, N-dimethylaminoethyl-N'-ethyl-carbodiimide and the like, and an activator, such as 1-hydroxybenzotriazole, 7-aza-1-hydroxybenzotriazole and the like, in an aprotic polar solvent such as dichloromethane, dimethylformamide and the like, at between 10°C and 100°C, preferably at 25°C, for 2 to 24 hours, preferably 8 to 16 hours. The nitro group of the phenylalanine is subjected to conditions to reduce the nitro group to an amine, in the case of Reaction Scheme III tin dichloride, in an aprotic solvent such as chloroform, dimethylformamide, dimethylacetamide, N-methylpyrrolidinone for 2 to 36 hours and preferably 16 hours at 20°C to 125°C, preferably at 25-30°C. The free amino group of the individual or mixtures of resin-bound aminophenylalanines is condensed with an aldehyde in the presence of a dieneophile, such as cyclopentadiene, cyclohexadiene and the like, and an acid such as trifluoroacetic acid or toluenesulfonic acid and the like, using in a polar solvent, such as dichloromethane, dimethylformamide, dimethylacetamide, N-methylpyrrolidinone or the like, for a period of 1 to 72 hours, usually 12 to

24 hours at 20°C to 75°C and preferably at 25°C to arrive at novel ttricyclic tetrahydroquinolinederivatives. Finally, the compounds can be cleaved from the resin by the methods common to those skilled in the art and the compounds tested for biological activity. It should be appreciated by those of skill in the art that with certain resins, cleavage from the resin results in the functional group on the resin coming off the resin and being maintained with the cleaved compounds. For example, with an amino-resin, such as methylbenzhydrylamine resin, the amine group from the resin is cleaved off the resin and makes the tricyclic tetrahydroquinoline(s) of interest an amide.

The term "functionalized resin" means any resin where functional groups have been introduced into the resin, as is common in the art. Such resins include, for example, those functionalized with amino, amide, or hydroxy groups. Such resins which can serve as solid supports are well known in the art and include, for example, 4-methylbenzhydrylamine-copoly(styrene-1% divinylbenzene) (MBHA), 4-hydroxymethylphenoxymethyl-copoly(styrene-1% divinylbenzene), 4-oxymethyl-phenyl-acetamido-copoly(styrene-1% divinylbenzene)(Wang), 4-(oxymethyl)phenylacetamido methyl (Pam), and Tentagel™, from Rapp Polymere Gmbh, trialkoxy-diphenyl-methyl ester-copoly-(styrene-1% divinylbenzene)(RINK) all of which are commercially available. Preparation of the combinatorial libraries can be by the "split resin approach." The split resin approach is described by, for example, U.S. Patent 5,010,175 to Rutter, WO PCT 91/19735 to Simon, and Gallop et al., J. Med. Chem., 37:1233-1251 (1994), all of which are incorporated herein by reference.

Exemplary amino carboxylic acids which can be used in the above Reaction Schemes include 2, 3, and 4-aminobenzoic acid, aminohippuric acid, 4'-aminophenylalanine, 4'-nitrophenylalanine, anthranilic acid (2-

aminobenzoic acid), 2-amino-4-chlorobenzoic acid, 2-amino-4-fluorobenzoic acid, 4-nitroanthranilic acid, 2-amino-5-bromobenzoic acid, 2-amino-5-chlorobenzoic acid, 2-amino-5-fluorobenzoic acid, 2-amino-5-iodobenzoic acid, 2-amino-5-methylbenzoic acid, 2-amino-6-methylbenzoic acid, 4,5-difluoroanthranilic acid, 3-amino-2-naphthoic acid, 4-aminobenzoic acid, 4-amino-2-chlorobenzoic acid, 4-amino-2-hydroxybenzoic acid, 4-amino-3-hydroxybenzoic acid, 4-amino-3-methoxybenzoic acid, and 4-amino-3-methylbenzoic acid. Additional amino benzoic acids or aminoaryl carboxylic acids are provided in the ensuing Examples.

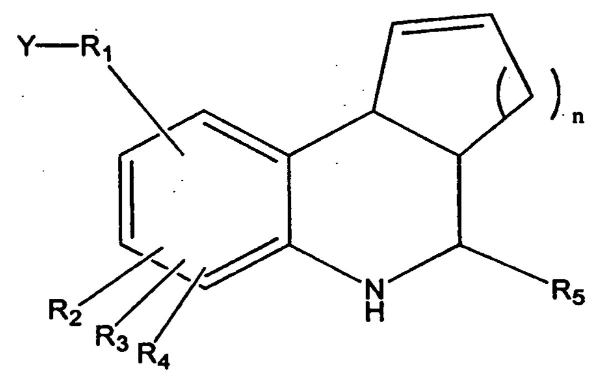
Exemplary aldehydes which can be used in the above reaction schemes I and II are glyoxylic acid, 1-napthaldehyde, 2,3,4-trifluorobenzaldehyde, 2,3,5-trichlorobenzaldehyde, 2,3-difluorobenzaldehyde, 2,4-dichlorobenzaldehyde, 2,5-difluorobenzaldehyde, 2,5-dimethylbenzaldehyde, 2,6-difluorobenzaldehyde, 2-bromobenzaldehyde, 2-chloro-5-nitrobenzaldehyde, 2-fluorobenzaldehyde, 3,4-(methylenedioxy)-6-nitrobenzaldehyde, 3,4-difluorobenzaldehyde, 3,5-bis(trifluoromethyl)benzaldehyde, 3,5-dichlorobenzaldehyde, 3-cyanobenzaldehyde, 3-fluorobenzaldehyde, 3-formylchromone, 3-nitro-4-chlorobenzaldehyde, 3-phenoxybenzaldehyde, 4-cyanobenzaldehyde, 4-pyridinecarboxaldehyde, 3-methoxy-2-nitro-benzaldehyde, 3-hydroxy-4-nitro-benzaldehyde. Additional aldehydes include the following: 2-nitrobenzaldehyde, 2, 4-dinitrobenzaldehyde, 4-methyl-2-nitrobenzaldehyde, 4,5-methylenedioxy-2-nitrobenzaldehyde, 5-ethyl-2-nitrobenzaldehyde, 4,5-dimethoxy-2-nitrobenzaldehyde, 5-chloro-2-nitrobenzaldehyde, 3-fluoro-2-nitrobenzaldehyde, 3-trifluoro-2-nitrobenzaldehyde, 4-(dimethylamino)-2-nitrobenzaldehyde, 3-methoxy-2-nitrobenzaldehyde, 5-hydroxy-2-nitrobenzaldehyde, 2,6-dinitrobenzaldehyde and the like.

Exemplary carboxylic acids which can be used in the above Reaction Schemes include, but are not limited to, acetic acid, butyric acid, cyclobutanecarboxylic acid, cycloheptanecarboxylic acid, cyclohexanebutyric acid, cyclohexanecarboxylic acid, cyclohexanepropionic acid, cyclohexylacetic acid, cyclopentanecarboxylic acid, cyclopentylacetic acid, hydrocinnamic acid, isobutyric acid, isovaleric acid, octanoic acid, propionic acid, tert-butylacetic acid, trimethylacetic acid, 1-adamantaneacetic acid, 4-methyl-1-cyclohexanecarboxylic acid, 4-methylcyclohexaneacetic acid, 4-methylvaleric acid, 2-ethyl-2-hexenoic acid, 2-ethylbutyric acid, 2-ethylhexanoic acid, 2-methylbutyric acid, 2-methylcyclopropanecarboxylic acid, 2-norbornaneacetic acid, 2-phenylbutyric acid, 2-propylpentanoic acid, 3,3,3-triphenylpropionic acid, 3,3-diphenylpropionic acid, 4-tert-butyl-cyclohexanecarboxylic acid, 3,5,5-trimethylhexanoic acid, 5-phenylvaleric acid, 3-(2-methoxyphenyl)propionic acid, 3-(3,4,5-trimethoxyphenyl)propionic acid, 3-(3,4-dimethoxyphenyl)propionic acid, heptanoic acid, 3-cyclopentylpropionic acid, formic acid, lauric acid, 3-methylvaleric acid, 3-phenylbutyric acid, α-cyclohexylphenylacetic acid, α-methylcinnamic acid, crotonic acid, ethoxyacetic acid, 4-chlorocinnamic acid, 4-ethoxyphenylacetic acid, m-tolylacetic acid, methoxyacetic acid, p-tolylacetic acid, phenoxyacetic acid, phenylacetic acid, tiglic acid, trans-3-hexenoic acid, trans-cinnamic acid, trans-styrylacetic acid, triphenylacetic acid, 4-fluorophenylacetic acid, vinylacetic acid, (2,5-dimethoxyphenyl)acetic acid, (2-naphthoxy)acetic acid, (3,4-dimethoxyphenyl)acetic acid, (α-α-α-trifluoro-m-tolyl)acetic acid, (methylthio)acetic acid, 1-(4-chlorophenyl)-1-cyclopentanecarboxylic acid, 1-naphthylacetic acid, 1-phenyl-1-cyclopropanecarboxylic acid, 4-isobutyl-α-methylphenylacetic acid, 4-methoxyphenylacetic acid, 2,4-hexadienoic acid, 2-(trifluoromethyl)-cinnamic acid, 2-chloro-4-fluorophenylacetic acid, 2-naphthylacetic acid, 99%, 3,4,5-trimethoxycinnamic acid, 3,4-dichlorophenylacetic acid, 3,4-dimethylbenzoic acid, 3,4,5-

trimethoxyphenylacetic acid, 3-benzoylpropionic acid, 3-bromophenylacetic acid, 3-fluorophenylacetic acid, 3-methoxyphenylacetic acid, 3-thiopheneacetic acid, 4-biphenylacetic acid, 4-bromophenylacetic acid, α,α,α-trifluoro-m-toluic acid, α,α,α-trifluoro-o-toluic acid, benzoic acid, niflumic acid, o-anisic acid, o-toluic acid, piperonylic acid, 1-napthoic acid, 2,3-dichlorobenzoic acid, 2,3-dimethoxybenzoic acid, 2,4-dichlorobenzoic acid, 2,4-difluorobenzoic acid, 2,4-dimethoxybenzoic acid, 2,4-dimethylbenzoic acid, 2,5-dichlorobenzoic acid, 2,5-dimethylbenzoic acid, 2,6-dichlorobenzoic acid, 2,6-difluorobenzoic acid, 2,6-dimethoxybenzoic acid, 2-bromobenzoic acid, 2-chloro-4,5-difluorobenzoic acid, 2-chlorobenzoic acid, 2-ethoxybenzoic acid, 2-fluorobenzoic acid, 2-napthoic acid, 3,4,5-triethoxybenzoic acid, 3,4,5-trimethoxybenzoic acid, 3,4-dichlorobenzoic acid, 3,4-difluorobenzoic acid, 3,4-dimethoxybenzoic acid, 3,5-bis(trifluoromethyl)-benzoic acid, 5-bromo-2-chlorobenzoic acid, 3,5-dimethyl-p-anisic acid, 3-bromobenzoic acid, 3-chlorobenzoic acid, 3-cyanobenzoic acid, 3-dimethylaminobenzoic acid, 3-fluoro-4-methylbenzoic acid, 3-fluorobenzoic acid, 3-iodo-4-methylbenzoic acid, 3-phenoxybenzoic acid, 4-chloro-o-anisic acid, α,α,α-trifluoro-p-toluic acid, 4-cyanobenzoic acid, 4-dimethylaminobenzoic acid, 4-ethoxybenzoic acid, Isonicotinic acid, 4-ethylbenzoic acid, m-anisic acid, m-toluic acid, nicotinic acid, p-anisic acid, p-toluic acid, picolinic acid, pyrrole-2-carboxylic acid, 4-fluorobenzoic acid, 4-isopropoxybenzoic acid, tetrahydro-2-furoic acid, tetrahydro-3-furoic acid, trans-3-(3-pyridyl)acrylic acid, xanthene-9-carboxylic acid, (4-pyridylthio)acetic acid, (phenylthio)acetic acid, 4-iodobenzoic acid, 4-isopropylbenzoic acid, 2-furoic acid, 2-pyrazinecarboxylic acid, 2-thiopheneacetic acid, 2-thiophenecarboxylic acid, 5-bromonicotinic acid, 3,5-dichlorobenzoic acid, 6-chloronicotinic acid, 3,5-dimethoxybenzoic acid, 3,5-dimethylbenzoic acid, chromone-2-carboxylic acid, 1-isoquinolinecarboxylic acid, 3-methyl-2-thiophenecarboxaldehyde, 4'-ethyl-4-biphenylcarboxylic acid, 4-(diethylamino)benzoic acid, 4-benzoylbenzoic acid,

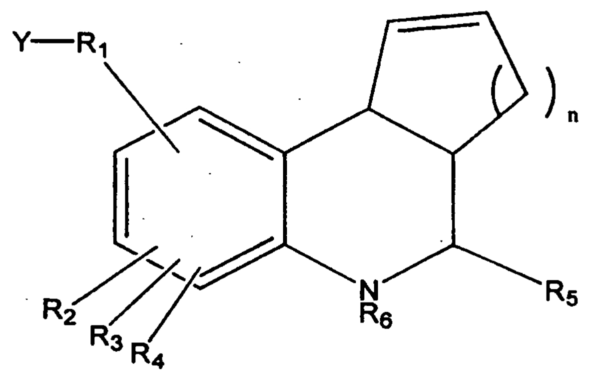
4-biphenylcarboxylic acid, 4-bromobenzoic acid, 4-butylbenzoic acid, 4-chlorobenzoic acid, additional acids include the following; acetyl chloride, phenoxyacetyl chloride, 4-chlorophenoxyacetyl chloride benzyloxyacetyl chloride and acetoxyacetyl chloride.

The tricyclic tetrahydroquinolines prepared by the above Reaction Schemes, once cleaved from the resin, result in compounds of Formula II:



Formula II

These tetrahydroquinoline compounds of Formula II can be converted, generally before cleavage from the resin, to alternatively substituted compounds having an alkyl or acyl, or other functionality as defined R^6 above and provided by Formula I:



Formula I

The tricyclic tetrahydroquinolines of Formula II, before cleavage from the resin, can be substituted at positions R^6 following Reaction Scheme IV provided in Figure 4. Briefly, as shown in Reaction Scheme IV, the tricyclic tetrahydroquinoline prepared by the above Reaction Schemes I, II or III (Reaction Scheme III repeated in Figure 4) is condensed with a carboxylic acid, carboxylic acid anhydride, acid halide, alkyl halide sulfonyl halide or isocyanate in an aprotic solvent, such as dimethylformamide, dichloromethane, 1-methyl-2- pyrrolidinone, N-N,-dimethylacetamide, tetrahydrofuran, dioxane and the like, in the presence of an acid acceptor, if desired, to furnish a substituted tricyclic tetrahydroquinoline.

For example, preparation of the library containing alternatively substituted tricyclic tetrahydroquinoline other than R^6 equal to a hydrogen atom involves, instead of cleaving from the resin, free NH of the newly formed tricyclic tetrahydroquinoline compound being reacted with a carboxylic acid activated with N-[(dimethylamino)-1H-1, 2, 3-triazolo[4,5-b]pyridin-1-ylmethylene]-N-

methylmethanaminium hexafluorophosphate N-oxide (HATU, PerSeptive Biosystems, Farmingham, MA), dissolved in dimethylformamide, N-N,-dimethylacetamide, 1-methyl-2- pyrrolidinone and the like. The reaction is allowed to proceed for 1 to 24 hours at 20°C to 80°C, preferably at 25°C for 3 to 5 hours to yield various carboxamide derivatives. Finally, the compounds are cleaved from the resin as described above and tested for biological activity.

Exemplary carboxylic acid, carboxylic acid anhydride, acid halide, alkyl halide or isocyanate which can be used include nalidixic acid,2-phenyl-4-quinolinecarboxylic acid, 2-pyrazinecarboxylic acid, niflumic acid, 4-nitrophenylacetic acid, 4-(-nitrophenyl)butyric acid, (3,4-dimethoxyphenyl)acetic acid, 3,4-(methylenedioxy)phenylacetic acid, 4-nitrocinnamic acid, 3,4,-(methylenedioxy)cinnamic acid, 3,4,5-trimethoxycinnamic acid, benzoic acid, 2-chlorobenzoic acid, 2-nitrobenzoic acid, 2-(p-toluoyl)benzoic acid, 2,4-dinitrophenylacetic acid, 3-(3,4,5-trimethoxyphenyl)-proprionic acid, 4-biphenylacetic acid, 1-napthylacetic acid, (2-napthoxy)acetic acid, trans-cinnamic acid, picolinic acid, 3-amino-4-hydroxybenzoic acid, (4-pyridylthio)acetic acid, 2,4-dichlorobenzoic acid, 3,4-dichlorobenzoic acid, 4-biphenylcarboxylic acid, thiophenoxyacetic acid, 1-benzoylpropionic acid, phenylacetic acid, hydrocinnamic acid, 3,3-diphenylpropionic acid, 3,3,3-triphenylpropionic acid, 4-phenylbutyric acid, phenoxyacetic acid, (+/-)-2-phenoxypropionic acid, 2,4-dimethoxybenzoic acid, 3,4-dimethoxybenzoic acid, 3,4-dihydroxybenzoic acid, 2,4-dihydroxybenzoic acid, 3,4,5-trimethoxybenzoic acid, 3,4,5-triethoxybenzoic acid, 3,4,5-trihydroxybenzoyl, 2-benzoylbenzoic acid, 1-napthoic acid, xanthene-9-carboxylic acid, 4-chloro-2-nitrobenzoic acid, 2-chloro-4-nitrobenzoic acid, 4-chloro-3-nitrobenzoic acid, 2-chloro-5-nitrobenzoic acid, 4-dimethylaminobenzoic acid, 4-(diethylamino)benzoic acid, 4-nitrobenzoic acid, 3-dimethylaminobenzoic

acid, p-toluic acid, p-anisic acid, trimethylacetic acid, tert-butylacetic acid, (-)-menthoxyacetic acid, cyclohexanecarboxylic acid, cyclohexylacetic acid, dicyclohexylacetic acid, cyclohexanebutyric acid, cycloheptanecarboxylic acid, abietic acid, acetic acid, octanoic acid, (methylthio)acetic acid, 3-nitropropionic acid, 4-amino-3 hydroxybenzoic acid, 2-methyl-4-nitro-1-imidizole propionic acid, 2-furoic acid, (s)(-)-2-pyrrolidone-5-carboxylic acid, (2-pyrimidylthio)acetic acid, 4-methoxy-2-quinolinecarboxylic acid, 1-adamantanecarboxylic acid, piperonylic acid, 5-methyl-3-phenylisoxazole-4-carboxylic acid, rhodanine-3-acetic acid, 2-norbornaneacetic acid, nicotinnic acid, 9-oxo-9H-thioxanthene-3-carboxylic acid 10,10 dioxide, 2-thiophenecarboxylic acid, 5-nitro-2-furoic acid, indole-3-acetic acid, isonicotinic acid, lithocholic acid, cholic acid, deoxycholic acid, hyodeoxycholic acid, Boc-L-Ala, Boc-L-Cys(Mob), Boc-L-Asp(Bzl), Boc-L-Glu(Bzl), Boc-L-Phe, Boc-Gly, Boc-L-His(Tos), Boc-L-Ile, Boc-L-Lys(Clz), Boc-L-Leu, Boc-Met(O), Boc-L-Asn, Boc-L-Pro, Boc-L-Gln, Boc-L-Arg(Tos), Boc-L-Ser(Bzl), Boc-L-Thr(Bzl), Boc-L-Val, Boc-L-Trp, Boc-L-Tyr(Brz), Boc-D-Ala, Boc-D-Cys(Mob), Boc-D-Asp(Bzl), Boc-D-Glu(Bzl), Boc-D-Phe, Boc-D-His(Dnp), Boc-D-Ile, Boc-D-Lys(Clz), Boc-D-Leu, Boc-D-Met(O), Boc-D-Asn, Boc-D-Pro, Boc-D-Gln, Boc-D-Arg(Tos), Boc-D-Ser(Bzl), Boc-D-Thr(Bzl), Boc-D-Val, Boc-D-Trp(CHO), Boc-D-Tyr(Brz), Boc-L-Met, 2-aminobutyric acid, 4-aminobutyric acid, 2-aminoisobutyric acid, L-norleucine, D-norleucine, 6-aminocaproic acid, 7-aminoheptanoic acid, thioproline, L-Norvaline, D-Norvaline, α-ornithine, methionyl sulfonyl, L-naphthyalanine, D-naphthyalanine, L-phenylglycine, D-phenylglycine, β-alanine, L-cyclohexylalanine, D-cyclohexylalanine, hydroxyproline, nitrophenylalanine, dehydroproline, 1,3-propane sultone, 1-propanesulfonyl chloride, 1-octanesulfonyl chloride, perfluoro-1-octanesulfonly fluoride, (+)-10-camphorsulfonyl chloride, (-)-10-camphorsulfonyl chloride,

benzenesulfonly chloride, 2-nitrobenzenesulfonyl chloride, p-toluenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, n-acetylsulfanilyl chloride, 2,5-dichlorobenzenesulfonyl chloride, 2,4-dinitrobenzenesulfonyl chloride, 2-mesitylenesulfonyl chloride, 2-napthalenesulfonyl chloride, phenylisocyanate, methylisocyanate and t-butyl isocyanate. Those abbreviations used above for amino acids and their protecting groups are ones commonly used in the field, each of which are identified, for example, in Stewart and Young, supra.

Pharmaceutical compositions and medicaments containing the new tricyclic tetrahydroquinoline derivatives are also included within the scope of the present invention as are methods of using the compounds and compositions. The new tricyclic tetrahydroquinoline compounds and libraries containing the same can be used for a variety of purposes and indications. For example, to evaluate whether the subject tricyclic tetrahydroquinolines have antimicrobial activity, and, therefore, can be used to treat infections, the ability of the compounds to inhibit bacterial growth can be determined by methods well known in the art. An exemplary in vitro antimicrobial activity assay is described in Blondelle and Houghten, Biochemistry, 30:4671-4678 (1991), which is incorporated herein by reference. In brief, Staphylococcus aureus ATCC 29213 (Rockville, MD) is grown overnight at 37°C in Mueller-Hinton broth, then re-inoculated and incubated at 37°C to reach the exponential phase of bacterial growth (i.e., a final bacterial suspension containing 10^5 to 5×10^5 colony-forming units/ml). The concentration of cells is established by plating 100 µl of the culture solution using serial dilutions (e.g., 10^{-2}, 10^{-3} and 10^{-4}) onto solid agar plates. In 96-well tissue culture plates tricyclic tetrahydroquinolines, individual or in mixtures, are added to the bacterial suspension at concentrations derived from serial two-fold dilutions ranging from 1500 to 2.9 µg/ml. The plates are incubated overnight at 37°C and the growth determined

at each concentration by OD_{620} nm. The IC_{50} (the concentration necessary to inhibit 50% of the growth of the bacteria) can then be calculated.

Additional assays can be used to test the biological activity of the instant tricyclic tetrahydroquinoline. Such as a competitive enzyme-linked immunoabsorbent assay and radio-receptor assays, both as described in greater detail below. The latter test, the radio-receptor assay, can be selective for either the μ, δ or κ opiate receptors and is therefore an indication of tricyclic tetrahydroquinolines' analgesic properties.

Competitive Enzyme-Linked Immunosorbent Assay (ELISA): The competitive ELISA method which can be used here is a modification of the direct ELISA technique described previously in Appel et al., J. Immunol. 144:976-983 (1990), which is incorporated herein by reference. It differs only in the MAb addition step. Briefly, multi-well microplates are coated with the antigenic peptide (Ac-GASPYPNLSNQQT-NH_2) at a concentration of 100 pmol/50 μl. After blocking, 25 μl of a 1.0 mg/ml solution of each ttricyclic tetrahydroquinolinemixture of a synthetic combinatorial library (or individual tricyclic tetrahydroquinoline) is added, followed by MAb 125-10F3 (Appel et al., supra) (25 μl per well). The MAb is added at a fixed dilution in which the tricyclic tetrahydroquinoline in solution effectively competes for MAb binding with the antigenic peptide adsorbed to the plate. The remaining steps are the same as for direct ELISA. The concentration of ttricyclic tetrahydroquinolinenecessary to inhibit 50% of the MAb binding to the control peptide on the plate (IC_{50}) is determined by serial dilutions of the tricyclic tetrahydroquinoline.

Radio-Receptor Assay: Particulate membranes can be prepared using a modification of the method described in Pasternak et al., Mol.

Pharmacol. 11:340-351 (1975), which is incorporated herein by reference. Rat brains frozen in liquid nitrogen can be obtained from Rockland (Gilbertsville, PA). The brains are thawed, the cerebella removed and the remaining tissue weighed. Each brain is individually homogenized in 40 ml Tris-HCl buffer (50 mM, pH 7.4, 4°C) and centrifuged (Sorvall® RC5C SA-600: Du Pont, Wilmington, DE) (16,000 rpm) for 10 mins. The pellets are resuspended in fresh Tris-HCl buffer and incubated at 37°C for 40 mins. Following incubation, the suspensions are centrifuged as before, the resulting pellets resuspended in 100 volumes of Tris buffer and the suspensions combined. Membrane suspensions are prepared and used in the same day. Protein content of the crude homogenates generally range from 0.15-0.2 mg/ml as determined using the method described in M.M. Bradford, M.M., Anal. Biochem. 72:248-254 (1976), which is incorporated herein by reference.

Binding assays are carried out in polypropylene tubes, each tube containing 0.5 ml of membrane suspension. 8 nM of ^{3}H-[D-Ala^2,Me-Phe^4,Gly-ol^5]enkephalin (DAMGO) (specific activity = 36 Ci/mmol, 160,000 cpm per tube; which can be obtained from Multiple Peptide Systems, San Diego, CA, through NIDA drug distribution program 271-90-7302) and 80 μg/ml of tricyclic tetrahydroquinoline, individual or as a mixture and Tris-HCl buffer in a total volume of 0.65 ml. Assay tubes are incubated for 60 mins. at 25°C. The reaction is terminated by filtration through GF-B filters on a Tomtec harvester (Orange, CT). The filters are subsequently washed with 6 ml of Tris-HCl buffer, 4°C. Bound radioactivity is counted on a Pharmacia Biotech Betaplate Liquid Scintillation Counter (Piscataway, NJ) and expressed in cpm. To determine inter- and intra-assay variation, standard curves in which ^{3}H-DAMGO is incubated in the presence of a range of concentrations of unlabeled DAMGO (0.13-3900 nM) are generally included in each plate of each assay (a 96-well format). Competitive inhibition assays are performed as above using

serial dilutions of the ttricyclic tetrahydroquinoline, individually or in mixtures. IC_{50} values (the concentration necessary to inhibit 50% of ^{3}H-DAMGO binding) are then calculated. As opposed to this μ receptor selective assay, assays selective for δ receptors can be carried out using [^{3}H]-Naltrindole (3 nM, specific activity 32 Ci/mmol as radioligand or, alternatively, assays selective for κ receptors can be carried out using [^{3}H]-U69,593 (3 nM, specific activity 62 Ci/mmol) as radioligand.

As pharmaceutical compositions for treating infections, pain, or any other indication the tricyclic tetrahydroquinoline compounds of the present invention are generally in a pharmaceutical composition so as to be administered to a subject at dosage levels of from 0.7 to 7000 mg per day, and preferably 1 to 500 mg per day, for a normal human adult of approximately 70 kg of body weight, this translates into a dosage of from 0.01 to 100 mg/kg of body weight per day. The specific dosages employed, however, can be varied depending upon the requirements of the patient, the severity of the condition being treated, and the activity of the compound being employed. The determination of optimum dosages for a particular situation is within the skill of the art.

For preparing pharmaceutical compositions containing compounds of the invention, inert, pharmaceutically acceptable carriers are used. The pharmaceutical carrier can be either solid or liquid. Solid form preparations include, for example, powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which can also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is generally a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active compound is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing pharmaceutical composition in the form of suppositories, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient-sized molds and allowed to cool and solidify.

Powders and tablets preferably contain between about 5% to about 70% by weight of the active ingredient. Suitable carriers include, for example, magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter and the like.

The pharmaceutical compositions can include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier, which is thus in association with it. In a similar manner, cachets are also included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid pharmaceutical compositions include, for example, solutions suitable for oral or parenteral administration, or suspensions, and emulsions suitable for oral administration. Sterile water solutions of the active

component or sterile solutions of the active component in solvents comprising water, ethanol, or propylene glycol are examples of liquid compositions suitable for parenteral administration.

Sterile solutions can be prepared by dissolving the active component in the desired solvent system, and then passing the resulting solution through a membrane filter to sterilize it or, alternatively, by dissolving the sterile compound in a previously sterilized solvent under sterile conditions.

Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably, the pharmaceutical composition is in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active tricyclic tetrahydroquinoline. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

The following Examples are intended to illustrate but not limit the present invention.

EXAMPLE 1

Combinatorial Library Of Tricyclic Tetrahydroquinoline Derivatives

This Example provides a representative solid-phase combinatorial synthesis of a library which contains approximately 2774 derivatives of tricyclic tetrahydroquinoline (THQs).

Following the above Reaction Scheme II, preparation of a library containing the THQs involves the following steps. Briefly, first, 19 diverse aminobenzoic acids, varying at position of Y-R^1, R^2, R^3 or R^4 without use of amino-protecting groups, were coupled to MBHA resin employing the tea-bag method of Houghten et. al, as described, for example in U.S. Patent No. 4,631,211 to Houghten and Houghten et al., Proc. Natl. Acad. Sci., 82:5131-5135 (1985), both of which are incorporated herein by reference. After coupling and thorough washing the 19 tea-bags, each containing one resin-bound aminobenzoic acid, were opened and the resin beads combined and thoroughly mixed in a large tea-bag as a suspension in dichloromethane (DCM). The resin mixture was dried under vacuum, then divided into equal portions and resealed in 73 labeled tea-bags, each tea-bag now containing a mixture of the 19 aminobenzoic acids. This was followed by reaction with 73 aldehydes, each differing by their R^5 substituent, and cyclopentadiene in the presence of trifluoroacetic acid. After washing with a series of solvents, the resins were dried under vacuum and the mixtures individually cleaved from the MBHA resin using a hydrogen fluoride (HF) procedure. The individual mixtures varying at Y-R^1, R^2, R^3 or R^4 and constant at R^5, each a mixture containing 38 individual compounds, including enantiomers, can then be tested for biological activity using any one of a variety of screening assays, such as those described above or others well known in the art.

The individual aminobenzoic acids which were used to prepare the library of 2770 THQs include the following: anthranilic acid, 2-amino-4-chlorobenzoic acid, 2-amino-4-fluorobenzoic acid, 4-nitroanthranilic acid, 2-amino-5-bromobenzoic acid, 2-amino-5-chlorobenzoic acid, 2-amino-5-fluorobenzoic acid, 2-amino-5-iodobenzoic acid, 2-amino-5-methylbenzoic acid, 2-amino-6-methylbenzoic acid, 4,5-difluoroanthranilic acid, 3-amino-2-naphthoic acid, 4-aminobenzoic acid, 4-amino-2-chlorobenzoic acid, 4-amino-2-hydroxybenzoic acid, 4-amino-3-hydroxybenzoic acid, 4-amino-3-methoxybenzoic acid, 4-amino-3-methylbenzoic acid, 4-aminohuppuric acid.

Individual aldehydes which can be employed are as follows: paraformldehyde, benzaldehyde, chloroacetaldehyde, cyclohexanecarboxaldehyde, d,l-glyceraldehyde, glyoxylic acid monohydrate, pyruvic aldehyde, salicylaldehyde, tribromoacetaldehyde, trimethylacetaldehyde, 1-methyl-2-pyrrolecarboxaldehyde, 1-napthaldehyde, 2,3,4-trifluorobenzaldehyde, 2,3,5-trichlorobenzaldehyde, 2,3-difluorobenzaldehyde, 2,4-dichlorobenzaldehyde, 2,5-difluorobenzaldehyde, 2,5-dimethylbenzaldehyde, 2,6-difluorobenzaldehyde, 2-bromobenzaldehyde, 2-chloro-5-nitrobenzaldehyde, 2-chloro-6-fluorobenzaldehyde, 2-cyanobenzaldehyde, 2-ethylbutyraldehyde, 2-fluorobenzaldehyde, 2-formylphenoxyacetic acid, 2-methoxy-1-naphthaldehyde, 2-nitro-5-chlorobenzaldehyde, 2-nitrobenzaldehyde, 2-pyridinecarboxaldehyde, 3,4-(methylenedioxy)-6-nitrobenzaldehyde, 3,4-difluorobenzaldehyde, 3,5-(trifluoromethyl)-bisbenzaldehyde, 3,5-dichlorobenzaldehyde, 3-benzaldehyde, 3-bromo-4-fluorobenzaldehyde, 3-bromobenzaldehyde, 3-carboxybenzaldehyde, 3-cyanobenzaldehyde, 3-fluorobenzaldehyde, 3-formylchromone, 3-furaldehyde, 3-hydroxybenzaldehyde, 3-nitro-4-chlorobenzaldehyde, 3-nitrobenzaldehyde, 3-phenoxybenzaldehyde, 3-phenylbutyraldehyde, 3-pyridinecarboxaldehyde, 4-bromo-2-

thiophenecarboxaldehyde, 4-bromobenzaldehyde, 4-carboxybenzaldehyde, 4-cyanobenzaldehyde, 4-fluorobenzaldehyde, 4-nitrobenzaldehyde, 4-pyridinecarboxaldehyde, 4-quinolinecarboxaldehyde, 5-bromosalicylaldehyde, 5-nitro-2-furaldehyde, 5-norbornene-2-carboxaldehyde, 6-methyl-2-pyridinecarboxaldehyde, 9-ethyl-3-carbazolecarboxaldehyde, 2,3-dimethylvaleraldehyde, 2,2-dimethyl-4-pentenal, 3-methoxy-2-nitro-benzaldehyde, 3-hydroxy-4-nitro-benzaldehyde, 2-methylbutyraldehyde, 2-methylvaleraldehyde, 4-chloro-3-nitro-benzaldehyde, trifluoro-p-tolualdehyde, 2-methylundecanal.

1. Coupling of Aminobenzoic Acids to MBHA Resin

Nineteen polypropylene mesh packets (tea-bags, ~3" square, 65μ; McMaster Carr, Chicago, IL) of (5 g, 0.89 meq/g) MBHA resin were prepared, washed with DCM (2X, ~ 5 ml each), neutralized with 5% diisopropylethylamine/ dichloromethane (DIEA/DCM) (3X, ~ 5 ml each), and washed with DCM (2X, ~ 5 ml each). Each resin packet was individually coupled overnight (~16 hrs) by adding 5X aminobenzoic acid (0.5 M)in 1:1 DMF/DCM solvent system followed by 5X diisopropylcarbodiimide (DIC) in DCM (0.5 M) and hydroxybenzotriazole (HOBt) (5X). Following coupling completion, resin packets were washed with DCM (2X), DMF (2X), and DCM (1X) and MeOH (1X). After drying under vacuum 4-12 hrs, each individual packet was then opened and the resin transfered to a large tea-bag (~5" square) which was sealed and shaken in DCM for 1 hour. After a MeOH wash the mixed resin was dried under vacuum and then 75 mg portions (calc. 73 mmole) distributed into labeled tea-bags (~1.5 " square) for use in subsequent chemistry.

2. Reaction of the Mixture of Resin-Bound Aminobenzoic Acids with Aldehydes and Cyclopentadiene

Three tea-bags (2x 75 mg aminobenzoic acid mixtures, and 35 mg 4-aminobenzoic acid resin) were added to each solution of 73 aldehydes (1 M) in DMF (15 mL) and cooled in freezer (-10 °C) for 15-30 minutes. After cooling, 2.5 mL of cyclopentadiene (2M final concentration) was added and the solution cooled in the freezer again for 15-30 minutes. Then 1.16 mL of trifluoroacetic (1M) was added and the cyclization reaction shaken for 45-50 hours at room temperature. Following completion of the tricylic tetrahydroquinoline formation, the resin packets were washed with DCM (2X), DMF (2X), and DCM (1X), MeOH (1X) and dried under vacuum.

3. Cleavage from the Resin

The tricyclic tetrahydroquinoline controls (4-aminobenzoic acid sibling bags) and mixtures were cleaved off the resin by treatment with HF (liquid (l)) at -15°C for 2 hrs in the presence of anisole scavenger followed by warming to room temperature while removing HF (gaseous (g)) with a nitrogen stream.

TABLE 1
Experimental Data for Aminobenzamide Controls

No.	Amide formed upon cleavage	Yield (mg)	Yield (%)	Calc. MW	Obs.* MW (M+1)	^{1}H NMR (d6-DMSO)
1	anthranilamide (2-amino-benzamide)	8.5	83	136.1	137.1	7.90 (b, 1H), 7.62 (d, 1H), 7.20-7.42 (b and dd, 2H), 6.88 (d, 1H), 6.75 (dd, 1H), 5.30 (vb)

TABLE 1
Experimental Data for Aminobenzamide Controls

No.	Amide formed upon cleavage	Yield (mg)	Yield (%)	Calc. MW	Obs.* MW (M+1)	^{1}H NMR (d6-DMSO)
2	2-amino-4-chlorobenzamide	9.8	77	170.6	171.1	7.80 (b, 1H), 7.52 (d, 1H), 7.15 (b, 1H), 6.71 (d, 1H), 6.47 (dd, 1H), 3.50 (vb, 2H)
3	2-amino-4-fluorobenzamide	6.2	54	154.1	155.1	7.70 (b, 1H), 7.47 (t, 1H), 7.08 (b, 1H), 6.42 (dd, 1H), 6.26 (ddd, 1H), 4.65 (vb, 2H)
4	4-nitro-anthranilamide	10.7	79	181.1	182.1	8.02 (b, 1H), 7.69 (d, 1H), 7.54 (d, 1H), 7.43 (b, 1H), 7.22 (dd, 1H), 4.45 (vb)
5	2-amino-5-bromobenzamide	11.2	69	215	215.1 216.9	7.83 (b, 1H), 7.66 (d, 1H), 7.29-7.13 (dd and b, 2H), 6.80-6.52 (b and d, 3H)
6	2-amino-5-chlorobenzamide	9.1	71	170.6	171.1	7.83 (b, 1H), 6.71 (d, 1H) 7.30-7.09 (b and dd, 2H), 7.77-7.60 (b and d, 3H)
7	2-amino-5-fluorobenzamide	8.8	76	154.1	155	7.80 (b, 1H), 7.43 (dd, 1H), 7.25 (b, 1H), 7.06 (ddd, 1H), 6.73 (dd, 1H), 4.97 (vb)
8	2-amino-5-iodobenzamide	14.1	72	262	262.9	7.93-7.78 (b and d, 2H), 7.38 (dd, 1H), 7.25 (b, 1H), 6.54 (d, 1H), 3.45 (vb, 2H)

TABLE 1
Experimental Data for Aminobenzamide Controls

No.	Amide formed upon cleavage	Yield (mg)	Yield (%)	Calc. MW	Obs.* MW (M+1)	¹H NMR (d6-DMSO)
9	2-amino-5-methylbenzamide	11.1	99	150.2	151.1	7.82 (b, 1H), 7.41 (s, 1H), 7.19 (b, 1H), 7.05 (dd, 1H), 6.70 (dd, 1H), 3.55 (vb), 2.17 (s, 3H)
10	2-amino-6-methylbenzamide	9.2	82	150.2	151.2	7.80 (b, 1H), 7.63 (b, 1H), 7.16 (dd, 1H), 6.69 (dd, 2H), 3.67 (vb), 2.27 (s, 3H)
11	4,5-difluoro-anthranilamide	4.4	34	172.1	173.1	7.78 (b, 1H), 7.63 (dd, 1H), 7.22 (b, 1H), 6.62 (dd, 1H), 3.70 (vb)
12	3-amino-2-naphthamide	9.4	67	186.2	187.1	8.17 (b and s, 2H), 7.95 (2, 1H), 7.76 (d, 1H), 7.60 (d, 1H), 7.58 (b, 1H) 738 (dd, 1H), 7.10 (dd, 1H), 7.08 (s, 1H)
13	4-aminobenzamide	9.5	93	136.1	137.3	7.64 (d, 2H), 6.65 (d, 1H), 5.10 (vb)
14	4-amino-2-chlorobenzamide	8.8	69	170.6	171.6	7.57 (b,1H), 7.22 (d, 2H), 6.63 (d, 1H), 6.53 (d, 1H), 4.10 (vb)
15	4-amino-2-hydroxybenzamide	10.4	91	152.1	153.3	7.60 (b,1H), 7.28 (s, 1H), 7.21 (d, 1H), 6.94 (b, 1H), 6.71 (d, 1H), 3.50 (vb)
16	4-amino-3-hydroxybenzamide	10	88	152.1	153.4	7.90 (b,1H), 7.50 (d, 1H), 6.11 (d, 1H), 6.05 (s, 1H), 5.35 (vb)

TABLE 1
Experimental Data for Aminobenzamide Controls

No.	Amide formed upon cleavage	Yield (mg)	Yield (%)	Calc. MW	Obs.* MW (M+1)	^{1}H NMR (d6-DMSO)
17	4-amino-3-methoxybenzamide	11	88	166.2	167.2	7.71 (b,1H), 7.41 (s, 1H), 7.36 (d, 1H), 7.11 (b, 1H), 6.80 (d, 1H), 4.70 (vb), 3.72 (s, 3H)
18	4-amino-3-methylbenzamide	9.2	82	150.2	151.3	7.75-7.48 (b and s and d, 3H), 6.94 (b, 1H), 6.75 (d, 1H), 4.60 (vb), 2.13 (s, 3H)
19	4-aminohippuric amide (N-(4-amino)-benzoyl-amino-acet-amide)	14.1	97	193.2	194.1	8.76 (b, 0.5H), 8.57 (b, 0.5H), 8.44 (b, 0.5H), 8.23 (b, 0.5H), 7.83 (dd, 2H), 7.62 (m, 4H), 7.33 (bd, 1H), 7.00 (bd, 1H), 6.62 (d, 2H)

*Obs. MW (M+1) = Observed MW (M+1)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
1	hydrogen	7.7	120	49.49 (l)	214.2	(ND) Not Determined	7.70-7.35 (m+s, 4H), 6.94 (m, 1H), 5.68 (dd, 1H), 5.62 (dd, 1H), 3.84 (dd, 1H), 2.95-2.40 (mm+DMSO, calc 4H), 2.22 (dd, 1H)
2	phenyl	7.8	90	2.16 (s)	290.4	291.4 (M+1)	7.70-6.50 (mm, 10H), 6.15 (b, 1H), 5.85 (dd, 1H), 5.55 (dd, 1H), 4.60 (dd, 1H), 4.04 (dd, 1H), 3.85-3.25 (mm+H2O, calc 2H), 2.90 (dd, 1H), 1.60 (m, 1H)
3	chloroacetyl	7.1	90	19.80 (s)	262.7	245.3 (-NH3)	7.73 (s, 1H), 7.36 (dd, 1H), 7.25-6.60 (mm, 3H), 6.62 (d, 1H), 5.92 (dd, 1H), 5.64 (dd, 1H), 3.93 (dd, 1H), 3.80-3.25 (mm+H2O, calc 4H), 2.88 (dd, 1H), 2.22 (m, 1H)
4	cyclohexane-carboxyl	7.2	81	55.79 (l)	296.4	297.4 (M+1)	7.65-7.30 (b+s+d, 3H), 6.81 (b, 1H), 6.67 (d, 1H), 5.85 (dd, 1H), 5.62 (dd, 1H), 5.38 (b, 1H), 3.85 (dd, 0.5H), 3.72 (m, 0.5H), 3.00 (dd, 0.5H), 2.82 (m, 0.5H), 2.28-0.85 (mm, 14H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
5	D,L-glyceryl	6	73	27.55 (l)	274.3	257.4 (-NH3)	7.78-7.30 (b+d, 2H), 7.25-6.60 (b+m, 2H), 6.60 (d, 1H), 6.15 (dd, 1H), 6.03 (dd, 1H), 4.41 (dd, 1H), 3.70 (m, 2H), 3.07 (d, 1H), 2.88 (m, 1H), 2.62 dd, 1H), 2.32-01.90 (mm, 3H)
6	carboxy	8.6	111	2.37 (s)	258.3	(ND)	7.70- 6.70 (mm, 6H), 5.85 (dd, 1H), 5.63 (dd, 1H), 4.05 (dd, 1H), 3.64 (d, 1H), 3.17 (ddd, 1H), 2.28 (m, 1H)
7	β-phenylcinnamyl	7.3	62	5.14 (s)	392.5	(ND)	7.70-6.55 (mm, 15H), 6.08 (b, 1H), 5.90 (m, 1H), 5.75 (m, 1H), 5.42 (d, 1H), 4.02 (dd, 1H), 3.00 (m, 1H), 2.62 (m, 1H), 2.14 (m, 1H)
8	acetyl	6.7	87	4.35 (s)	256.3	(ND)	7.85 (s, 1H), 7.70-6.85 (m, 5H), 5.82 (m, 1H), 5.74 (m, 1H), 3.90 (m, 1H), 3.00-2.50 (mm,calc. 6H), 2.22 (m, 1H)
9	2-hydroxyphenyl	9.2	100	37.93 (l)	306.4	307.5 (M+1)	7.70-6.55 (mm, 10H), 5.92 (dd, 1H), 5.58 (dd, 1H), 4.82 (d, 1H), 4.04 (dd, 1H), 3.70 (m, 2H), 3.15 (ddd, 1H), 1.62 (m, 1H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
10	tribromoacetyl	8.2	59	4.00 (s)	465	387.2 (-Br)	7.70-6.55 (mm, 5H), 6.17 (d, 1H), 5.98 (dd, 1H), 5.70 (dd, 1H), 3.98 (dd, 1H), 3.90 (dd, 1H), 3.60 (m, 2H), 3.12 (ddd, 1H), 2.25 (m, 1H)
11	trimethylacetyl	6.2	76	4.31 (s)	270.4	271.4 (M+1)	7.65-7.30 (mm, 3H), 6.95-6.70 (mm, 2H), 5.92 (dd, 1H), 5.68 (dd, 1H), 5.45 (b, 1H), 3.90 (dd, 1H), 3.80-3.10 (mm+ H20, calc2H), 82 (ddd, 1H), 2.23 (m, 1H), 1.25-0.88 (m+s, 10H)
12	1-napthyl	6.1	60	4.60 (s)	340.4	(ND)	8.32 (m, 1H), 8.10-7.45 (mm, 9H), 7.15 (b, 1H), 6.94 (b, 1H), 6.18 (b, 1H), 5.94 (m, 1H), 5.58 (m, 1H), 5.42 (d, 1H), 4.24 (dd, 1H), 3.28 (m, 1H), 1.55 (m, 1H)
13	2,3,4-trifluorophenyl	9.5	92	4.49 (s)	344.3	345.3 (M+1)	7.65 (s, 1H), 7.50-7.25 (mm, 4H), 6.95 (b, 1H), 6.82 (b, 1H), 6.72 (d, 1H), 6.26 (b, 1H), 5.90 (dd, 1H), 5.58 (dd, 1H), 4.84 (d, 1H), 4.08 (dd, 1H), 2.98 (ddd, 1H), 2.34 (m, 1H), 1.72 (m, 1H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
14	2,3,5-trichlorophenyl	5.6	47	5.10 (s)	393.7	395.3 (M+2)	7.85 (s, 1H), 7.70-7.53 (mm, 3H), 7.45 (d, 1H), 6.97 (b, 1H), 6.80 (b, 1H), 6.71 (d, 1H), 6.19 (b, 1H), 5.93 (dd, 1H), 5.59 (dd, 1H), 4.88 (d, 1H), 4.08 (dd, 1H), 2.98 (m, 1H), 2.34 (m, 1H), 1.64 (m, 1H)
15	2,3-difluorophenyl	6.7	68	48.19 (l)	326.4	327.3 (M+1)	7.70-6.65 (mm, 8H), 6.15 (b, 1H), 5.90 (dd, 1H), 5.58 (dd, 1H), 4.88 (s, 1H), 4.08 (dd, 1H), 3.04 (m, 1H), 1.70 (m, 1H)
16	2,4-dichlorophenyl	9	84	4.84 (s)	359.3	(ND)	7.70-7.35 (mm, 4H), 6.90 (b, 1H), 6.80 (d, 1H), 6.12 (b, 1H), 5.92 (dd, 1H), 5.58 (dd, 1H), 4.84 (s, 1H), 4.08 (dd, 1H), 3.05 (m, 1H), 1.62 (m, 1H)
17	2,5-difluorophenyl	8.4	86	4.32 (s)	342.8	343.3	7.65 (s, 1H), 7.53-7.10 (mm, 5H), 6.95 (b, 1H), 6.80 (b, 1H), 6.70 (d, 1H), 6.14 (b, 1H), 5.88 (dd, 1H), 5.58 (dd, 1H), 4.80 (d, 1H), 4.05 (dd, 1H), 2.98 (ddd, 1H), 2.36 (ddd, 1H), 1.68 (ddd, 1H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
18	2,5-dimethylphenyl	7.9	83	4.60 (s)	318.4	319.3 (M+1)	7.65 (s, 1H), 7.40 (d, 1H), 7.30 (s, 1H), 7.10-6.75 (mm, 4H), 6.66 (d, 1H), 5.95 (b, 1H), 5.88 (dd, 1H), 5.58 (dd, 1H), 4.72 (s, 1H), 4.04 (dd, 1H), 2.96 (m, 1H), 2.45-2.15 (m+s, 7H), 1.60 (ddd, 1H)
19	2,6-difluorophenyl	8.6	88	4.08 (s)	326.4	327.2 (M+1)	7.68 (s, 1H), 7.40 (d, 1H), 7.20-6.70 (mm, 5H), 6.64 (d, 1H), 6.34 (b, 1H), 5.88 (dd, 1H), 5.60 (dd, 1H), 4.94 (s, 1H), 4.06 (dd, 1H), 2.94 (m, 1H), 2.64 (m, 1H), 1.98 (m, 1H)
20	2-bromophenyl	9	81	4.59 (s)	369.3	(ND)	7.70-7.15 (mm, 7H), 6.85 (b, 1H), 6.70 (d, 1H), 6.14 (b, 1H), 5.92 (dd, 1H), 5.60 (dd, 1H), 4.82 (s, 1H), 4.05 (dd, 1H), 3.10 (m, 1H), 1.60 (m, 1H)
21	2-chloro-5-nitrophenyl	8.1	73	4.40 (s)	369.8	370.2 (M+1)	8.40 (s, 1H), 8.20 (d, 1H), 7.80 (d, 1H), 7.58 (s, 1H), 7.42 (d, 1H), 6.98 (b, 1H), 6.82 (b, 1H), 6.72 (d, 1H), 6.28 (b, 1H), 5.94 (dd, 1H), 5.58 (dd, 1H), 4.92 (s, 1H), 4.10 (dd, 1H), 3.12 (m, 1H), 2.35 (m, 1H), 1.60 (ddd, 1H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
22	2-chloro-6-fluorophenyl	9	88	4.28 (s)	342.8	343.3 (M+1)	7.70-6.45 (mm, 8H), 5.94-5.84 (b+dd, 2H), 5.64 (dd, 1H), 5.08 (s, 1H), 4.05 (dd, 1H), 3.05 (m, 1H), 1.90 (m, 1H)
23	2-cyanophenyl	8.6	91	2.59 (s)	315.4	(ND)	8.42 (m, 1H), 8.20-6.70 (mm, 8H), 6.28 (b, 1H), 5.92 (m, 1H), 5.65 (m, 1H), 3.95 (s, 1H), 2.88 (m, 1H), 2.25 (m, 1H), 1.20 (m, 1H)
24	2-ethylbutyryl	7.5	88	4.63 (s)	284.4	285.3 (M+1)	7.70-6.65 (mm, 5H), 5.88 (dd, 1H), 5.64 (dd, 1H), 5.34 (s, 1H), 3.90 (dd, 1H), 3.25 (m, 1H), 2.80 (m, 1H), 2.25 (m, 1H), 1.80-0.70 (mm, 10H)
25	2-fluorophenyl	7.7	83	4.23 (s)	308.4	309.2 (M+1)	7.70-7.10 (mm, 6H), 6.96 (b, 1H), 6.80 (b, 1H), 6.70 (d, 1H), 6.18 (b, 1H), 5.88 (dd, 1H), 5.56 (dd, 1H), 4.82 (s, 1H), 4.05 (dd, 1H), 2.96 (m, 1H), 2.35 (m, 1H), 1.64 (ddd, 1H)
26	2-nitro-5-chlorophenyl	7	63	4.35 (s)	369.8	370.2 (M+1)	8.05 (d, 1H), 7.85 (m, 1H), 7.70-7.45 (mm, 3H), 7.15 (b, 1H), 6.94 (b, 1H), 6.65 (d, 1H), 6.55 (d, 1H),6.20 (b, 1H), 5.94 (dd, 1H), 5.55 (dd, 1H), 4.98 (s, 1H), 4.05 (dd, 1H), 3.05 (m, 1H), 1.90 (m, 1H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
27	2-nitrophenyl	6.9	69	4.14 (s)	335.4	(ND)	8.05-7.45 (mm, 6H), 7.00 (b, 1H), 6.84 (b, 1H), 6.70 (d, 1H), 6.60 (d, 1H), 6.20 (b, 1H), 6.00 (dd, 1H), 5.65 (dd, 1H), 4.94 (s, 1H), 4.05 (dd, 1H), 3.10 (m, 1H), 1.75 (m, 1H)
28	3,4-(methylenedioxy)-6-nitrophenyl	9.2	81	4.13 (s)	379.4	380.3 (M+1)	7.73-7.25 (mm, 4H), 6.95 (b, 1H), 6.82 (b, 1H), 6.72 (d, 1H), 6.35 (b, 1H), 6.28 (d, 2H), 5.95 (dd, 1H), 5.62 (dd, 1H), 4.94 (d, 1H), 4.04 (dd, 1H), 3.08 (m, 1H), 2.58 (m, 1H), 1.65 (ddd, 1H)
29	3,4-difluorophenyl	10	102	49.10 (l)	326.4	327.2 (M+1)	7.75-7.15 (mm, 6H), 7.05 (b, 1H), 6.82 (b, 1H), 6.72 (d, 1H), 6.20 (s, 1H), 5.96 (dd, 1H), 5.70 (dd, 1H), 4.64 (s, 1H), 4.07 (dd, 1H), 2.94 (m, 1H), 1.68 (ddd, 1H)
30	3,5-bis-(trifluoromethyl)-phenyl	10.6	83	4.95 (s)	426.4	427.3 (M+1)	8.12 (s, 2H), 8.05 (s, 1H), 8,00 (d, 1H), 7.60 (s, 1H), 7.45 (d, 1H), 7.00 (b, 1H), 6.80 (b, 1H), 6.70 (d, 1H), 6.35 (s, 1H), 5.92 (dd, 1H), 5.06 (dd, 1H), 4.85 (d, 1H), 4.05 (dd, 1H), 3.05 (ddd, 1H), 2.30 (m, 1H), 1.55 (m, 1H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
31	3,5-dichlorophenyl	8.2	76	4.82 (s)	359.3	359.2	7.70-7.30 (mm, 6H), 7.00 (b, 1H), 6.78 (b, 1H), 6.74 (d, 1H), 6.20 (s, 1H), 5.94 (dd, 1H), 5.62 (dd, 1H), 4.65 (s, 1H), 4.05 (dd, 1H), 2.98 (m, 1H), 1.70 (ddd, 1H)
32	3-(3,4-dichloro-phenoxy)phenyl	4.8	35	5.55 (s)	451.4	451.1	7.70-6.65 (mm, 10H), 6.68 (d, 1H), 6.15 (b, 1H), 5.90 (dd, 1H), 5.56 (dd, 1H), 4.60 (s, 1H), 4.02 (dd, 1H), 2.96 (m, 1H), 2.34 (m, 1H), 1.68 (m, 1H)
33	3-(4-methoxy-phenoxy)phenyl	10.6	86	4.86 (s)	412.5	(ND)	7.70-6.55 (mm, 13H), 6.16 (b, 1H), 5.95 (m, 1H), 5.62 (m, 1H), 4.58 (d, 1H), 4.04 (dd, 1H), 3.68 (s, 3H), 2.94 (m, 1H), 2.32 (m, 1H), 1.62 (m, 1H)
34	3-(4-methyl-phenoxy) phenyl	7.8	66	5.08 (s)	396.2	(ND)	7.65-6.50 (mm, 13H), 6.18 (b, 1H), 5.94 (m, 1H), 5.62 (m, 1H), 4.62 (d, 1H), 4.04 (dd, 1H), 3.68 (s, 3H), 2.94 (m, 1H), 2.32 (m, 1H), 1.62 (m, 1H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
35	3-bromo-4-fluorophenyl	13.4	115	4.61 (s)	387.3	387.2 389.1	7.80-7.25 (mm, 4H), 6.92 (b, 1H), 6.80 (b, 1H), 6.70 (d, 1H), 6.22 (b, 1H), 5.90 (dd, 1H), 5.58 (dd, 1H), 4.62 (d, 1H), 4.02 (dd, 1H), 2.94 (ddd, 1H), 2.32 (ddd, 1H), 1.65 (ddd, 1H)
36	3-bromophenyl	9.3	84	4.51 (s)	369.3	(ND)	7.95-7.15 (mm, 7H), 7.05 (b, 1H), 6.82 (b, 1H), 6.70 (d, 1H), 6.24 (s, 1H), 5.95 (dd, 1H), 5.60 (dd, 1H), 4.64 (d, 1H), 4.08 (dd, 1H), 2.94 (m, 1H), 1.68 (m, 1H)
37	3-carboxyphenyl	9.9	99	3.56 (s)	334.4	335.2 (M+1)	8.05 (s, 1H), 7.80 (d, 1H), 7.75-7.42 (mm, 4H), 6.90 (b, 1H), 6.85 (b, 1H), 6.68 (d, 1H), 6.20 (b, 1H), 5.92 (dd, 1H), 5.55 (dd, 1H), 4.66 (s, 1H), 4.05 (dd, 1H), 2.94 (m, 1H), 2.35 (m, 1H), 1.60 (ddd, 1H)
38	3-cyanophenyl	10.8	114	3.95 (s)	315.4	(ND)	8.00-7.25 (mm, 7H), 7.00 (b, 1H), 6.80 (b, 1H), 6.72 (d, 1H), 6.24 (s, 1H), 5.95 (dd, 1H), 5.60 (dd, 1H), 4.70 (d, 1H), 4.10 (dd, 1H), 3.00 (m, 1H), 1.65 (m, 1H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
39	3-fluorophenyl	9.1	98	4.24 (s)	308.4	309.3 (M+1)	7.65-6.64 (mm, 9H), 6.15 (b, 1H), 5.90 (dd, 1H), 5.55 (dd, 1H), 4.62 (d, 1H), 4.04 (dd, 1H), 2.94 (m, 1H), 2.35 (m, 1H), 1.62 (m, 1H)
40	3-chromone	8.7	81	3.86 (s)	358.3	(ND)	8.38 (s, 1H), 8.12 (d, 1H), 7.90-7.40 (mm, 7H), 7.05 (b, 1H), 6.86 (b, 1H), 6.70 (d, 1H), 5.95 (m, 2H), 5.62 (dd, 1H), 4.72 (s, 1H), 4.08 (dd, 1H), 3.15 (m, 1H), 1.95 (m, 1H)
41	3-hydroxyphenyl	9.4	102	3.52 (s)	306.4	(ND)	7.65-6.45 (mm, 10H), 6.10 (b, 1H), 5.92 (dd, 1H), 5.58 (dd, 1H), 4.50 (d, 1H), 4.02 (dd, 1H), 2.88 (m, 1H), 1.68 (m, 1H)
42	3-methoxyphenyl	10	104	4.16 (s)	320.4	(ND)	7.62-6.50 (mm, 9H), 6.12 (b, 1H), 5.90 (dd, 1H), 5.58 (dd, 1H), 4.62 (m, 1H), 4.05 (m, 1H), 2.92 (m, 1H), 2.40-2.15 (m+s, 4H), 1.72 (m, 1H)
43	3-methylphenyl	6.5	71	4.43 (s)	304.4	(ND)	7.60-6.45 (mm, 9H), 6.12 (b, 1H), 5.88 (dd, 1H), 5.56 (dd, 1H), 4.55 (d, 1H), 4.02 (dd, 1H), 2.90 (m, 1H), 2.40-1.90 (mm, 5H), 1.60 (m, 1H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
44	3-nitro-4-chlorophenyl	9.4	85	4.33 (s)	369.8	370.2 (M+1)	8.08 (s, 1H), 7.78 (s, 2H), 7.65 (s, 1H), 7.44 (s, 1H), 6.95 (b, 1H), 6.80 (b, 1H), 6.30 (b, 1H), 5.92 (dd, 1H), 5.58 (dd, 1H), 4.72 (d, 1H), 4.04 (dd, 1H), 3.00 (m, 1H), 2.30 (ddd, 1H), 1.65 (ddd, 1H)
45	3-nitrophenyl	8.4	83	4.13 (s)	335.4	(ND)	8.50 (d, 1H), 8.15 (dd, 1H), 7.90 (d, 1H), 7.72-7.52 (mm, 3H), 7.42 (d, 1H), 7.00 (b, 1H), 6.83 (b, 1H), 6.70 (d, 1H), 6.32 (s, 1H), 5.92 (dd, 1H), 5.55 (dd, 1H), 4.68 (d, 1H), 4.05 (dd, 1H), 3.05 (ddd, 1H), 2.32 (ddd, 1H), 1.60 (m, 1H)
46	3-phenoxyphenyl	9.2	80	4.88 (s)	382.5	382.4	7.70-6.60 (mm, 10H), 6.14 (b, 1H), 5.92 (dd, 1H), 5.58 (dd, 1H), 4.60 (d, 1H), 4.04 (dd, 1H), 2.90 (m, 1H), 2.30 (m, 1H), 1.65 (m, 1H)
47	2-phenylpropyl	10.3	103	3.59 (s)	332.5	(ND)	8.28 (s, 1H), 8.16 (d, 1H), 8.02 (d, 1H), 7.65-6.75 (mm, 6H), 7.42 (d, 1H), 6.64 (d, 0.5H), 6.45 (d, 0.5H), 5.84 (dd, 1H), 5.62 (m, 1H), 4.55 (m,0.5H), 4.32 (m, 1H), 3.75-3.00 (mm+ H_2O, calc. 5H), 2.24 (m, 2H), 1.80-1.10 (mm, 7H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
48	3-pyridine-carboxyl	7.5	86	(ND)	291.4	(ND)	8.72 (s, 1H), 8.55 (d, 1H), 8,00 (d, 1H), 7.65-7.35 (mm, 3H), 7.00 (b, 1H), 6.76 (b, 1H), 6.70 (d, 1H), 6.28 (s, 1H), 5.94 (dd, 1H), 5.06 (dd, 1H), 4.72 (d, 1H), 4.05 (dd, 1H), 3.00 (m, 1H), 2.30 (m, 1H), 1.64 (m, 1H)
49	4-bromo-2-thiophene-carboxyl	5.8	52	4.47 (s)	375.3	375.2 377.2	8.10-6.50 (mm, 8H), 5.90 (dd, 1H), 5.62 (dd, 1H), 4.85 (d, 1H), 4.02 (dd, 1H), 3.15 (m, 1H), 2.85 (m, 1H), 1.90 (m, 1H)
50	4-bromophenyl	8.7	79	4.62 (s)	369.3	369.4 371.1	7.85-6.45 (mm, 10H), 6.15 (b, 1H), 5.92 (dd, 1H), 5.58 (dd, 1H), 4.68 (d, 1H), 4.02 (dd, 1H), 2.88 (m, 1H), 2.45 (m, 1H), 1.68 (m, 1H)
51	4-carboxyphenyl	10.3	103	35.05 (l)	334.4	335.3 (M+1)	7.92 (s, 2H), 8.05 (s, 1H), 8.00 (d, 1H), 7.60 (s, 1H), 7.45 (d, 1H), 7.02 (b, 1H), 6.82 (b, 1H), 6.70 (d, 1H), 6.25 (b, 1H), 5.92 (dd, 1H), 5.58 (dd, 1H), 4.68 (s, 1H), 4.05 (dd, 1H), 2.95 (ddd, 1H), 2.34 (m, 1H), 1.60 (m, 1H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
52	4-cyanophenyl	8.3	88	3.98 (s)	315.4	(ND)	7.85 (d, 2H), 7.70-7.50 (mm, 3H), 7.45 (d, 1H), 7.08 (b, 1H), 6.82 (b, 1H), 6.68 (d, 1H), 6.25 (b, 1H), 5.90 (dd, 1H), 5.55 (dd, 1H), 4.70 (s, 1H), 4.05 (dd, 1H), 2.95 (m, 1H), 2.30 (m, 1H), 1.55 (m, 1H)
53	4-fluorophenyl	9.5	103	4.20 (s)	308.4	309.4 (M+1)	7.80-6.68 (mm, 9H), 6.20 (b, 1H), 5.94 (dd, 1H), 5.58 (dd, 1H), 4.62 (s, 1H), 4.04 (dd, 1H), 2.90 (ddd, 1H), 2.35 (m, 1H), 1.62 (m, 1H)
54	4-methoxy-1-naphthyl	9.2	83	4.60 (s)	370.5	(ND)	8.20 (m, 1H), 7.88-6.45 (mm, 11H), 5.90 (m, 1H), 5.68 (m, 1H), 3.95 (s, 3H), 3.18 (m, 1H), 2.10 (m, 1H), 1.62 (m, 1H)
55	4-nitrophenyl	7.7	77	4.16 (s)	335.4	336.2 (M+1)	8.24 (d, 2H), 7.70 (d, 2H), 7.58 (s, 1H), 7.45 (d, 1H), 6.95 (b, 1H), 6.80 (b, 1H), 6.70 (d, 1H), 6.30 (b, 1H), 5.92 (dd, 1H), 5.55 (dd, 1H), 4.75 (s, 1H), 4.06 (dd, 1H), 2.98 (ddd, 1H), 2.32 (ddd, 1H), 1.56 (ddd, 1H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds
[2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
56	4-pyridine-carboxyl	8.2	94	1.81 (s)	291.4	292.4 (M+1)	8.85 (b, 2H), 7.70 (b, 2H), 7.50 (s, 1H), 7.45 (d, 1H), 6.98 (b, 1H), 6.82 (b, 1H), 6.74 (dd, 1H), 6.30 (b, 1H), 5.94 (dd, 1H), 5.58 (dd, 1H), 4.72 (s, 1H), 4.08 (dd, 1H), 3.05 (m, 1H), 2.30 (m, 1H), 1.62 (m, 1H)
57	4-quinoline-carboxyl	10	98	2.42 (s)	341.4	342.2 (M+1)	8.45 (d, 2H), 8.12 (d, 2H), 7.92-7.58 (m, 6H), 7.45 (d, 1H), 6.95 (b, 1H), 6.75 (d, 1H), 6.24 (b, 1H), 5.96 (dd, 1H), 5.52 (dd+s, 2H), 4.24 (dd, 1H), 3.15 (m, 1H), 2.32 (m, 1H), 1.42 (ddd, 1H)
58	5-bromo-2-hydroxyphenyl	10.3	89	4.12 (s)	385.3	(ND)	7.90-6.50 (mm, 9H), 5.88 (dd, 1H), 5.58 (dd, 1H), 4.75 (d, 1H), 4.00 (dd, 1H), 3.10 (ddd, 1H), 2.30 (m, 1H), 1.60 (m, 1H)
59	5-nitro-2-furyl	35.1	360	3.78 (s)	325.3	326.2 (M+1)	7.72 (1, 2H), 7.60 (s, 1H), 7.45 (d, 1H), 7.15-6.58 (mm, 4H), 6.36 (b, 1H), 5.88 (dd, 1H), 5.60 (dd, 1H), 4.72 (d, 1H), 4.05 (dd, 1H), 3.10 (ddd, 1H), 2.40 (m, 1H), 2.10 (m, 1H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
60	5-norbornen-2-yl	7.2	78	5.38 (s)	306.4	(ND)	7.50 (s, 1H), 7.38 (d, 1H), 7.20-6.65 (mm, 6H), 5.88 (dd, 1H), 5.65 (dd, 1H), 3.90 (dd, 1H), 3.22 (m, 1H), 3.10-2.10 (mm+DMSO, calc. 5 H), 1.80-1.25 (mm, 4H)
61	1,2-dimethylbutyl	7.5	84	4.88 (s)	298.4	299.4 (M+1)	7.58 (b, 1H), 7.48 (s, 1H), 7.35 (d, 1H), 6.85 (b, 1H), 6.72 (d, 1H), 5.88 (dd, 1H), 5.65 (dd, 1H), 5.33 (b, 1H), 3.90 (dd, 1H), 3.12 (m, 1H), 2.78 (m, 1H), 2.22 (m, 2H), 1.85 (m, 1H), 1.60-0.70 (mm, 12H)
62	1,1-dimethyl-3-butyl	7.7	87	4.37 (s)	296.4	(ND)	8.15 (s, 1H), 7.78 (s, 1H), 7.60-30 (m, 4H), 6.82 (b, 2H), 6.70 (d, 1H), 6.52 (d, 1H), 5.90 (dd, 1H), 5.62 (dd, 1H), 3.85 (dd, 1H), 2.80 (m, 1H), 2.20 (m, 1H), 1.75 (m, 1H), 1.35-0.85 (mm, 8H)
63	3-methoxy-2-nitrophenyl	7.8	71	4.18 (s)	365.4	366.2 (M+1)	7.68-7.15 (mm, 5H), 6.95 (b, 1H), 6.82 (b, 1H), 6.75 (d, 1H), 6.24 (b, 1H), 5.88 (dd, 1H), 5.58 (dd, 1H), 4.38 (d, 1H), 3.95 (dd, 1H), 3.85 (s, 3H), 2.78 (ddd, 1H), 2.35 (m, 1H), 1.68 (ddd, 1H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
64	3-hydroxy-4-nitrophenyl	7.9	75	4.10 (s)	351.4	352.1 (M+1)	7.90 (d, 1H), 7.58 (s, 1H), 7.42 (d, 1H), 7.20 (s, 1H), 7.04 (d, 1H), 6.92 (b, 1H), 6.80 (b, 1H), 6.68 (d, 1H), 6.22 (b, 1H), 5.94 (dd, 1H), 5.56 (d, 1H), 4.60 (s, 1H), 4.04 (dd, 1H), 2.92 (m, 1H), 2.32 (m, 1H), 1.64 (m, 1H)
65	2-methylbutyryl	7.1	88	4.34 (s)	270.4	271.3	7.80 (b, 1H), 7.45 (s, 1H), 7.36 (d, 1H), 6.75 (b, 2H), 6.68 (d, 1H), 5.85 (dd, 1H), 5.61 (dd, 1H), 3.86 (dd, 1H), 3.03 (dd, 1H), 2.78 (m, 1H), 2.22 (ddd, 1H), 1.75-0.75 (mm, 10H)
66	1-methylbutyl	7.9	93	4.60 (s)	284.4	285.3 (M+1)	7.60 (b, 1H), 7.45 (s, 1H), 7.38 (d, 1H), 6.75 (b, 2H), 6.70 (d, 1H), 5.88 (dd, 1H), 5.63 (dd, 1H), 3.88 (dd, 1H), 3.05 (dd, 1H), 2.80 (m, 1H), 2.22 (m, 1H), 1.70-0.80 (mm, 12H)
67	4-chloro-3-nitro-phenyl	8.3	75	4.37 (s)	369.8	370.2 (M+1)	8.12 (s, 1H), 7.80 (s, 2H), 7.60 (s, 1H), 7.40 (d, 1H), 6.94 (b, 1H), 6.80 (b, 1H), 6.70 (d, 1H), 6.26 (b, 1H), 5.92 (dd, 1H), 5.56 (d, 1H), 4.70 (d, 1H), 4.04 (dd, 1H), 2.98 (ddd, 1H), 2.30 (ddd, 1H), 1.65 (ddd, 1H)

TABLE 2: Experimental Data for Tricylic Tetrahydroquinoline Control Compounds [2-Substituted-3,4-(1'-propenyl)-6-carboxamide quinoline]

No.	2-Substituent (R^1)	Yield (mg)	% Yield	HPLC RT [25 cm (l) or 5 cm (s) column]	Calc. MW	MW Found (MALDI)	NMR (d, DMSO)
68	trifluoro-p-toluyl	10.9	101	4.61 (s)	358.4	359.0 (M+1)	7.85-7.45 (mm, 6H), 7.08 (b, 1H), 6.84 (b, 1H), 6.68 (d, 1H), 6.25 (b, 1H), 5.92 (dd, 1H), 5.58 (dd, 1H), 4.72 (s, 1H), 4.08 (dd, 1H), 2.95 (m, 1H), 2.34 (m, 1H), 1.60 (m, 1H)
69	1-methyldecanyl	5.5	50	6.47 (s)	368.6	(ND)	7.60 (b, 1H), 7.45 (s, 1H), 7.35 (d, 1H), 6.75 (b, 2H), 6.70 (d, 1H), 6.50 (b, 1H), 5.85 (dd, 1H), 5.64 (b, 1H), 3.88 (dd, 1H), 3.05 (dd, 1H), 2.80 (m, 1H), 2.20 (m, 1H), 1.65-0.75 (mm, 24H)

EXAMPLE 2

Combinatorial Library Of Branched Tricyclic Tetrahydroquinoline Derivatives

This Example provides a representative solid-phase combinatorial synthesis of a library which contains approximately 17,000 derivatives of branched tricylic tetrahydroquinolines (THQs).

Following the above Reaction Scheme III, preparation of a library containing the THQs involved the following steps. Briefly, first, L or D N-BOC p-nitrophenylalanine was attached to MBHA resin using tea-bags. After removal of the BOC protecting group, the nitrogen was acylated with 170 acid diverse derivatives creating a variation of the R^8 substitent, which, again employed the tea-bags to carry out the operations. The acylated products were seperated into four new subsets (42 or 43 acids per group) by appropriate resin mixing techniques and the nitro group converted to an amino functionality by reduction. The 8 subgroups (L or D branch, four acid sets) were distributed into tea-bags and reacted with 25 aldehydes and cyclopentadiene in the presence of trifluoroacetic acid to generate new tricylic tetrahydroquinoline derivatives. After standard HF cleavage, the individual mixtures varying at R^8 and constant at Y-R^1 and R^5, each a mixture containing either 84 or 86 individual compounds, including enantiomers, which can then be tested for biological activity.

The individual acids which were be used to prepare with a library of 17,000 TTHQs include the following: acetic acid, butyric acid, cyclobutanecarboxylic acid, cycloheptanecarboxylic acid, cyclohexanebutyric acid, cyclohexanecarboxylic acid, cyclohexanepropionic acid, cyclohexylacetic acid, cyclopentanecarboxylic acid, cyclopentylacetic acid, hydrocinnamic acid, isobutyric acid, isovaleric acid, octanoic acid, propionic acid, tert-butylacetic acid, trimethylacetic acid, 1-adamantaneacetic acid, 4-methyl-1-cyclohexanecarboxylic acid, 4-methylcyclohexaneacetic acid, 4-methylvaleric acid, 2-ethyl-2-hexenoic acid, 2-ethylbutyric acid, 2-ethylhexanoic acid, 2-methylbutyric acid, 2-methylcyclopropanecarboxylic acid, 2-norbornaneacetic acid,

2-phenylbutyric acid, 2-propylpentanoic acid, 3,3,3-triphenylpropionic acid, 3,3-diphenylpropionic acid, 4-tert-butyl-cyclohexanecarboxylic acid, 3,5,5-trimethylhexanoic acid, 5-phenylvaleric acid, 3-(2-methoxyphenyl)propionic acid, 3-(3,4,5-trimethoxyphenyl)propionic acid, 3-(3,4-dimethoxyphenyl)propionic acid, heptanoic acid, 3-cyclopentylpropionic acid, formic acid, lauric acid, 3-methylvaleric acid, 3-phenylbutyric acid, α-cyclohexylphenylacetic acid, α-methylcinnamic acid, crotonic acid, ethoxyacetic acid, 4-chlorocinnamic acid, 4-ethoxyphenylacetic acid, m-tolylacetic acid, methoxyacetic acid, p-tolylacetic acid, phenoxyacetic acid, phenylacetic acid, tiglic acid, trans-3-hexenoic acid, trans-cinnamic acid, trans-styrylacetic acid, triphenylacetic acid, 4-fluorophenylacetic acid, vinylacetic acid, (2,5-dimethoxyphenyl)acetic acid, (2-naphthoxy)acetic acid, (3,4-dimethoxyphenyl)acetic acid, (α-α-α-trifluoro-m-tolyl)acetic acid, (methylthio)acetic acid, 1-(4-chlorophenyl)-1-cyclopentanecarboxylic acid, 1-naphthylacetic acid, 1-phenyl-1-cyclopropanecarboxylic acid, 4-isobutyl-α-methylphenylacetic acid, 4-methoxyphenylacetic acid, 2,4-hexadienoic acid, 2-(trifluoromethyl)-cinnamic acid, 2-chloro-4-fluorophenylacetic acid, 2-naphthylacetic acid, 3,4,5-trimethoxycinnamic acid, 3,4-dichlorophenylacetic acid, 3,4-dimethylbenzoic acid, 3,4,5-trimethoxyphenylacetic acid, 3-benzoylpropionic acid, 3-bromophenylacetic acid, 3-fluorophenylacetic acid, 3-methoxyphenylacetic acid, 3-thiopheneacetic acid, 4-biphenylacetic acid, 4-bromophenylacetic acid, α,α,α-trifluoro-m-toluic acid, α,α,α-trifluoro-o-toluic acid, benzoic acid, niflumic acid, o-anisic acid, o-toluic acid, piperonylic acid, 1-napthoic acid, 2,3-dichlorobenzoic acid, 2,3-dimethoxybenzoic acid, 2,4-dichlorobenzoic acid, 2,4-difluorobenzoic acid, 2,4-dimethoxybenzoic acid, 2,4-dimethylbenzoic acid, 2,5-dichlorobenzoic acid, 2,5-dimethylbenzoic acid, 2,6-dichlorobenzoic acid, 2,6-difluorobenzoic acid, 2,6-dimethoxybenzoic acid, 2-bromobenzoic acid, 2-chloro-4,5-difluorobenzoic acid, 2-chlorobenzoic acid, 2-ethoxybenzoic acid, 2-fluorobenzoic acid, 2-napthoic acid, 3,4,5-triethoxybenzoic acid, 3,4,5-trimethoxybenzoic acid, 3,4-dichlorobenzoic acid, 3,4-difluorobenzoic acid, 3,4-dimethoxybenzoic acid, 3,5-bis(trifluoromethyl)-benzoic acid, 5-bromo-2-chlorobenzoic acid, 3,5-dimethyl-p-anisic acid, 3-bromobenzoic acid, 3-chlorobenzoic acid, 3-cyanobenzoic acid, 3-dimethylaminobenzoic acid, 3-fluoro-4-methylbenzoic

acid, 3-fluorobenzoic acid, 3-iodo-4-methylbenzoic acid, 3-phenoxybenzoic acid, 4-chloro-o-anisic acid.

Individual aldehydes which were employed are as follows: glyoxylic acid monohydrate, 1-napthaldehyde, 2,3,4-trifluorobenzaldehyde, 2,3,5-trichlorobenzaldehyde, 2,3-difluorobenzaldehyde, 2,4-dichlorobenzaldehyde, 2,5-difluorobenzaldehyde, 2,5-dimethylbenzaldehyde, 2,6-difluorobenzaldehyde, 2-bromobenzaldehyde, 2-chloro-5-nitrobenzaldehyde, 2-fluorobenzaldehyde, 3,4-(methylenedioxy)-6-nitrobenzaldehyde, 3,4-difluorobenzaldehyde, 3,5-bis(trifluoromethyl)benzaldehyde, 3,5-dichlorobenzaldehyde, 3-cyanobenzaldehyde, 3-fluorobenzaldehyde, 3-formylchromone, 3-nitro-4-chlorobenzaldehyde, 3-phenoxybenzaldehyde, 4-cyanobenzaldehyde, 4-pyridinecarboxaldehyde, 3-methoxy-2-nitro-benzaldehyde, 3-hydroxy-4-nitro-benzaldehyde.

1. Coupling of L or D p-nitrophenylalanine to MBHA Resin

Polypropylene mesh packets (tea-bags, ~5") of (5 g each, 0.89 meq/g) MBHA resin were prepared, washed with DCM (2X, ~ 25 ml each), neutralized with 5% diisopropylethylamine/dichloromethane (DIEA/DCM) (3X, ~ 25 ml each), and washed with DCM (2X, ~ 25 ml each). Each resin packet set was individually coupled 2-4 hrs by adding 2.5X L or D N-BOC p-nitrobenzoic acid (0.5 M) in 1:1 DMF/DCM solvent system followed by 2.5X diisopropyl-carbodiimide (DIC) in DCM (0.5 M) and HOBt (2.5X). Following coupling completion, resin packets were washed with DCM (2X), DMF (2X), and DCM (1X) and MeOH (1X). The N-BOC protecting group was removed by shaking the bags with a solution of 55% TFA in DCM at room temperature for 30 mins. The liquid was decanted and the packets were washed with DCM (3X), 5% DIEA in DCM (3X) DCM (3X) After drying under vacuum 4-12 hrs, each individual packet was opened and the resin transfered in 75 mg (calc. 63 mmole) or 30 mg (calc. 25 mmole) portions to a small labeled tea-bags (~1.5" square) for use in subsequent chemistry.

2. Acylation of L or D p-nitrophenylalanine.

The resin packets (2X 75 mg and a 30 mg) were individually coupled with 170 different acids overnight (~16 hrs) by adding 5X acid (0.5 M) in 1:1 DMF/DCM solvent system followed by 5X diisopropylcarbodiimide (DIC) in DCM (0.5 M) and HOBt (5X). Following coupling completion, resin packets were washed with DCM (2X), DMF (2X), and DCM (1X) and MeOH (1X). The 30 mg bags from each of the 170 acid reactions were cleaved by standard HF procedures and the products analyzed (See Table 3). One of the 75 mg bags from each acid reaction was opened and combined into one of four large tea-bags (~ 5" square) and each then mixed in DCM for 30 min. After drying under vacuum, the resin-bound acid mixture sets were distributed in 30 mg portions into 1" tea-bags for use in subsequent chemistry.

TABLE 3
Experimental Data for N-Acetoylated 4-Nitrophenylalanine

No.	N-acetoyl substituent (R^1)	HPLC RT (25 cm (l) or 5 cm (s) column)	Expected MW	Observed MW
1	acetyl	21.77 (l)	251.31	(ND)Not Determined
2	α-cyclohexylphenylacetyl	43.60 (l)	409.33	(ND)
3	α-methylcinnamoyl	37.03 (l)	353.4	(ND)
4	α,α,α-trifluoro-m-toluoyl	37.12 (l)	381.33	(ND)
5	α,α,α-trifluoro-o-toluoyl	34.18 (l)	381.33	(ND)
6	α,α,α-trifluoro-p-toluoyl	37.92 (l)	381.33	(ND)
7	benzoyl	30.99 (l)	313.31	(ND)
8	butyroyl	27.14 (l)	279.32	(ND)
9	crotonoyl	26.52 (l)	277.3	(ND)
10	cyclobutanecarboxoyl	29.65 (l)	291.33	(ND)
11	cycloheptanecarboxoyl	35.88 (l)	333.41	(ND)

TABLE 3
Experimental Data for N-Acetoylated 4-Nitrophenylalanine

No.	N-acetoyl substituent (R^1)	HPLC RT (25 cm (l) or 5 cm (s) column)	Expected MW	Observed MW
12	cyclohexanebutyroyl	41.29 (l)	361.51	(ND)
13	cyclohexanecarboxoyl		319.41	(ND)
14	cyclohexanepropionoyl	38.72 (l)	347.43	(ND)
15	cyclohexylacetoyl	35.32 (l)	333.41	(ND)
16	cyclopentanecarboxoyl	30.82 (l)	305.35	(ND)
17	cyclopentylacetoyl	33.48 (l)	319.38	(ND)
18	ethoxyacetoyl	2.04 (s)	295.32	(ND)
19	4-chlorocinnamoyl	3.90 (s)	373.82	(ND)
20	4-cyanobenzoyl	3.22 (s)	338.34	(ND)
21	hydrocinnamoyl	34.00 (l)	341.41	(ND)
22	4-(dimethylamino)benzoyl	3.11 (s)	356.4	(ND)
23	4-ethoxybenzoyl	3.53 (s)	357.39	(ND)
24	isobutyroyl	26.86 (l)	279.32	(ND)
25	isonicotinoyl	21.51 (l)	314.32	(ND)
26	4-ethoxyphenylacetoyl	3.47 (s)	371.41	(ND)
27	isovaleroyl	29.78 (l)	293.34	(ND)
28	4-ethylbenzoyl	3.71 (s)	341.39	**341.9**
29	m-anisoyl	32.11 (l)	343.36	(ND)
30	m-toluoyl	33.73 (l)	327.36	(ND)
31	m-tolylacetoyl	34.29 (l)	341.39	(ND)
32	methoxyacetoyl		281.29	(ND)
33	nicotinoyl	22.09 (l)	314.31	(ND)
34	niflumoyl	4.32 (s)	473.43	(ND)
35	o-anisoyl	4.51 (s)	343.36	**343.9**
36	o-toluoyl	32.03 (l)	327.36	(ND)
37	octanoyl	4.17 (s)	335.42	(ND)

TABLE 3 Experimental Data for N-Acetoylated 4-Nitrophenylalanine				
No.	**N-acetoyl substituent (R^1)**	**HPLC RT (25 cm (l) or 5 cm (s) column)**	**Expected MW**	**Observed MW**
38	p-anisoyl	32.16 (l)	343.41	(ND)
39	p-toluoyl	33.65 (l)	327.41	(ND)
40	p-tolylacetoyl	34.28 (l)	341.39	(ND)
41	phenoxyacetoyl	3.62 (s)	343.36	**343.9**
42	phenylacetoyl	3.44 (s)	327.41	(ND)
43	picolinoyl	3.22 (s)	314.32	**315.0(M+1)**
44	piperonoyl	31.23 (l)	357.34	(ND)
45	propionoyl	2.62 (s)	261.25	(ND)
46	pyrrole-2-carboxyl	2.90 (s)	302.31	(ND)
47	4-fluoro-α-methylphenylacetoyl	4.74 (s)	359.38	**359.8**
48	4-fluorobenzoyl	3.29 (s)	331.32	(ND)
49	4-fluorophenylacetoyl	2.80 (s)	345.35	(ND)
50	tert-butylacetoyl	32.57 (l)	307.41	(ND)
51	tetrahydro-2-furoyl	2.61/2.68 (s)	307.33	**307.9**
52	tetrahydro-3-furoyl	2.39/2.45 (s)	307.33	**307.9**
53	tigloyl	3.17 (s)	291.33	(ND)
54	trans-3-(3-pyridyl)acroyl		340.36	(ND)
55	trans-3-hexenoyl	32.34 (l)	305.35	(ND)
56	trans-cinnamoyl		339.41	(ND)
57	trans-styrylacetoyl	34.80 (l)	353.4	(ND)
58	trimethylacetoyl	40.52 (l)	293.31	**294.0 (M+1)**
59	triphenylacetoyl	4.89 (s)	479.54	(ND)
60	4-isobutyl-α-methylphenylacetoyl	3.33 (s)	397.5	(ND)
61	vinylacetoyl	26.32 (l)	277.3	(ND)
62	xanthene-9-carboxyl	3.57 (s)	417.44	(ND)
63	(2,5-dimethoxyphenyl)acetoyl		387.41	(ND)

TABLE 3
Experimental Data for N-Acetoylated 4-Nitrophenylalanine

No.	N-acetoyl substituent (R^1)	HPLC RT (25 cm (l) or 5 cm (s) column)	Expected MW	Observed MW
64	(2-naphthoxy)acetoyl	3.84 (s)	393.42	(ND)
65	(3,4-dimethoxyphenyl)acetoyl	29.03 (l)	387.41	(ND)
66	(4-pyridylthio)acetoyl	19.81 (l)	360.41	**361.2 (M+1)**
67	(α-α-α-trifluoro-m-tolyl)acetoyl		395.36	(ND)
68	(methylthio)acetoyl	2.68 (s)	297.35	(ND)
69	(phenylthio)acetoyl	3.51 (s)	359.42	(ND)
70	1-(4-chlorophenyl)-1-cyclopentanecarboxoyl	27.83/28.67 (l)	415.9	**416**
71	1-adamantaneacetoyl	40.50 (l)	385.48	(ND)
72	1-naphthylacetoyl	3.90 (s)	377.42	(ND)
73	1-napthoyl	3.64 (s)	363.39	**363.8**
74	1-phenyl-1-cyclopropanecarboxoyl	38.07 (l)	353.4	(ND)
75	4-iodobenzoyl	3.79 (s)	439.23	(ND)
76	4-isopropoxybenzoyl	4.38 (s)	371.41	(ND)
77	2,3-dichlorobenzoyl	35.78 (l)	382.22	(ND)
78	4-methoxyphenylacetoyl	3.94 (s)	357.39	(ND)
79	2,3-dimethoxybenzoyl	3.61 (s)	373.39	(ND)
80	2,4-dichlorobenzoyl	36.44 (l)	382.22	(ND)
81	2,4-difluorobenzoyl	3.40 (s)	349.32	(ND)
82	4-methyl-1-cyclohexanecarboxoyl	3.21 (s)	333.41	(ND)
83	2,4-dimethoxybenzoyl	33.78 (l)	373.39	(ND)
84	2,4-dimethylbenzoyl	3.78 (s)	341.39	(ND)
85	2,4-hexadienoyl	3.42 (s)	303.34	(ND)
86	2,5-dichlorobenzoyl	3.82 (s)	382.22	(ND)
87	2,5-dimethylbenzoyl	3.76 (s)	341.39	(ND)
88	2,6-dichlorobenzoyl	3.58 (s)	382.22	**381.9**
89	2,6-difluorobenzoyl	3.35 (s)	349.31	(ND)

TABLE 3
Experimental Data for N-Acetoylated 4-Nitrophenylalanine

No.	N-acetoyl substituent (R^1)	HPLC RT (25 cm (l) or 5 cm (s) column)	Expected MW	Observed MW
90	4-methylcyclohexaneacetoyl	3.84 (s)	347.44	(ND)
91	2,6-dimethoxybenzoyl	3.37 (s)	373.39	(ND)
92	2-(trifluoromethyl)-cinnamoyl	4.27 (s)	407.37	(ND)
93	4-methylvaleroyl	3.33 (s)	307.37	(ND)
94	2-bromobenzoyl	3.52 (s)	392.23	(ND)
95	2-chloro-4,5-difluorobenzoyl	3.83 (s)	383.76	(ND)
96	2-chloro-4-fluorophenylacetoyl	3.70 (s)	379.8	(ND)
97	2-chlorobenzoyl	3.47 (s)	347.78	(ND)
98	2-ethoxybenzoyl	3.67 (s)	357.39	(ND)
99	2-ethyl-2-Hexenoyl	4.03 (s)	333.41	(ND)
100	2-ethylbutyroyl	3.41 (s)	307.37	(ND)
101	(+/-)-2-ethylhexanoyl	3.99 (s)	335.42	(ND)
102	2-fluorobenzoyl	3.47 (s)	331.32	(ND)
103	2-furoyl	3.03 (s)	303.29	(ND)
104	4-hydroxyquinoline-2-carboxyl		380.38	(ND)
105	(+/-)-2-methylbutyroyl	3.10 (s)	293.34	(ND)
106	2-methylcyclopropane-carboxyl	3.10 (s)	291.33	(ND)
107	2-naphthylacetoyl	3.91 (s)	377.42	(ND)
108	2-napthoyl	3.78 (s)	363.39	(ND)
109	2-norbornaneacetoyl	3.86 (s)	345.41	(ND)
110	2-phenylbutyroyl	3.88 (s)	355.41	(ND)
111	2-propylpentanoyl	3.96 (s)	335.42	(ND)
112	2-pyrazinecarboxoyl	2.74 (s)	315.31	(ND)
113	2-thiopheneacetoyl	3.32 (s)	333.38	(ND)
114	3,3,3-triphenylpropionoyl	4.60 (s)	493.59	(ND)
115	3,3-diphenylpropionoyl	4.26 (s)	417.51	(ND)

TABLE 3
Experimental Data for N-Acetoylated 4-Nitrophenylalanine

No.	N-acetoyl substituent (R^1)	HPLC RT (25 cm (l) or 5 cm (s) column)	Expected MW	Observed MW
116	3,4,5-triethoxybenzoyl	4.16 (s)	445.51	(ND)
117	3,4,5-trimethoxybenzoyl	3.45 (s)	403.41	(ND)
118	3,4,5-trimethoxycinnamoyl	3.69 (s)	429.45	(ND)
119	3,4-dichlorobenzoyl	4.17 (s)	382.22	(ND)
120	3,4-dichlorophenylacetoyl		396.61	(ND)
121	3,4-difluorobenzoyl	3.71 (s)	349.32	(ND)
122	4-imidazolecarboxoyl		303.3	(ND)
123	4-tert-butyl-cyclohexanecarboxoyl	4.32 (s)	375.49	375.9
124	3,4-dimethoxybenzoyl	3.29 (s)	373.41	(ND)
125	3,4-dimethylbenzoyl	3.77 (s)	341.39	(ND)
126	3,5,5-trimethylhexanoyl	4.21 (s)	349.45	(ND)
127	3,5-bis(trifluoromethyl)-benzoyl	4.49 (s)	449.33	(ND)
128	5-bromo-2-chlorobenzoyl	3.65 (s)	426.67	(ND)
129	5-bromonicotinoyl	3.18 (s)	393.22	(ND)
130	5-phenylvaleroyl	3.80 (s)	369.44	(ND)
131	3,5-dichlorobenzoyl	4.18 (s)	382.22	(ND)
132	6-chloronicotinoyl	3.10 (s)	348.77	(ND)
133	3,5-dimethoxybenzoyl		372.39	(ND)
134	3,5-dimethyl-p-anisoyl	3.82 (s)	371.41	(ND)
135	3,5-dimethylbenzoyl	3.79 (s)	341.39	(ND)
136	3-(2-methoxyphenyl)propionoyl	3.53 (s)	371.41	(ND)
137	3-(3,4,5-trimethoxyphenyl)-propionoyl	3.43 (s)	431.47	(ND)
138	3,4,5-trimethoxyphenylacetoyl	3.21 (s)	417.44	(ND)
139	3-(3,4-dimethoxyphenyl)-propionoyl	3.35 (s)	401.44	(ND)
140	heptanoyl	3.61 (s)	321.4	(ND)
141	3-benzoylpropionoyl	3.52 (s)	369.4	(ND)

TABLE 3
Experimental Data for N-Acetoylated 4-Nitrophenylalanine

No.	N-acetoyl substituent (R^1)	HPLC RT (25 cm (l) or 5 cm (s) column)	Expected MW	Observed MW
142	3-bromobenzoyl	3.87 (s)	392.23	(ND)
143	3-bromophenylacetoyl	3.79 (s)	406.26	(ND)
144	chromone-2-carboxyl	3.29 (s)	381.36	(ND)
145	5-methyl-2-pyrazinecarboxoyl		329.34	(ND)
146	3-chlorobenzoyl	3.61 (s)	347.78	(ND)
147	3-cyanobenzoyl	3.42 (s)	338.34	(ND)
148	3-cyclopentylpropionoyl	3.89 (s)	333.41	(ND)
149	3-(dimethylamino)benzoyl	2.58 (s)	356.4	(ND)
150	3-fluoro-4-methylbenzoyl	3.80 (s)	345.35	(ND)
151	3-fluorobenzoyl	3.52 (s)	331.32	(ND)
152	3-fluorophenylacetoyl	3.50 (s)	345.35	(ND)
153	6-methoxy-α-methyl-2-napthaleneacetoyl		421.48	(ND)
154	3-iodo-4-methylbenzoyl	4.18 (s)	453.26	(ND)
155	formyl		237.24	(ND)
156	6-methylnicotinoyl		328.35	(ND)
157	1-isoquinolinecarboxoyl	3.47 (s)	364.35	(ND)
158	lauryl	4.98 (s)	391.53	(ND)
159	3-methoxyphenylacetoyl	3.25 (s)	357.39	(ND)
160	3-methyl-2-thiophenecarboxoyl	3.28 (s)	333.39	(ND)
161	3-methylvaleroyl	3.48 (s)	307.37	(ND)
162	3-phenoxybenzoyl	4.05 (s)	405.43	(ND)
163	3-phenylbutyroyl	3.57 (s)	355.41	(ND)
164	3-thiopheneacetoyl	3.15 (s)	333.38	(ND)
165	4'-ethyl-4-biphenylcarboxoyl		417.49	(ND)
166	4-(diethylamino)benzoyl	2.76 (s)	384.45	(ND)
167	4-benzoylbenzoyl	3.79 (s)	417.44	(ND)

TABLE 3
Experimental Data for N-Acetoylated 4-Nitrophenylalanine

No.	N-acetoyl substituent (R^1)	HPLC RT (25 cm (l) or 5 cm (s) column)	Expected MW	Observed MW
168	4-biphenylacetoyl	3.91 (s)	403.46	(ND)
169	4-biphenylcarboxoyl	4.01 (s)	389.41	(ND)
170	4-bromobenzoyl	3.61 (s)	392.23	(ND)
171	4-bromophenylacetoyl	3.56 (s)	406.26	(ND)
172	4-butylbenzoyl	4.20 (s)	369.44	(ND)
173	4-chloro-o-anisoyl	3.71 (s)	377.8	(ND)
174	4-chlorobenzoyl	3.53 (s)	347.78	(ND)

3. Reduction of the Mixtures of Resin-Bound L or D N-Acylated p-nitrophenylalanine

All of the tea-bags from the previous step were placed in a large container shaken with a solution of $SnCl_2 \cdot 2H_2O$ in DMF (2.0 M, 1.5 L) at room temperature overnight (~16 hrs). The packets were washed with DMF (3X), methanol (2X), DCM (2X), air-dried for 30 min and then dried under vacuum for 1-2 hrs. The bags were sorted into appropriate sets for use in the subsequent chemistry.

4. Reaction and Cleavage of the Mixtures of Resin-Bound L or D N-Acylated p-Aminophenylalanine with Aldehydes and Cyclopentadiene

Following the procedure in Example 1 nine 30-mg tea-bags (L or D Series of 4 sets of acid mixtures, and 1 sibling bag containing L-N-propyl p-aminophenylalanine) were added to each solution of 25 aldehydes (1 M) in DMF (15 mL) and cooled in freezer (-10°C) for 15-30 minutes. After cooling, 2.5 mL of cyclopentadiene (2M final concentration) was added and the solution cooled in the freezer again for 15-30 minutes. Then 1.16 mL of trifluoroacetic (1M) was added and the cyclization reaction shaken for 45-50 hours at room temperature. Following

completion of the tricylic tetrahydroquinoline formation, the resin packets were washed with DCM (2X), DMF (2X), and DCM (1X), MeOH (1X) and dried under vacuum.

The tricyclic tetrahydroquinoline controls (L-N-propyl p-aminophenylalanine sibling bags) and mixtures were cleaved off the resin by treatment with HF (liquid (l)) at -15°C for 2 hrs in the presence of anisole followed by warming to room temperature while removing HF (gaseous (g)) with a nitrogen stream.

TABLE 4
Experimental Data for Tricylic Tetrahydroquinoline Controls

No.	2-Substituent (R^2)	HPLC RT (5 cm column)	Yield (mg)	Yield (%)
1	carboxy	2.06	8.2	86
2	1-napthyl	4.29	8.1	72
3	2,3,4-trifluorophenyl	4.31	9.7	86
4	2,3,5-trichlorophenyl	4.94	8.1	64
5	2,3-difluorophenyl	4.15	11.2	103
6	2,4-dichlorophenyl	4.67	10	86
7	2,5-difluorophenyl	4.17	10	92
8	2,5-dimethylphenyl	4.13	8.9	84
9	2,6-difluorophenyl	3.64	9.8	90
10	2-bromophenyl	4.37	11.9	100
11	2-chloro-5-nitrophenyl	4.24	7	59
12	2-fluorophenyl	3.94	9.5	91
13	3,4-(methylenedioxy)-6-nitrophenyl	4	10.9	89
14	3,4-difluorophenyl	4.14	9.9	91
15	3,5-bis(trifluoromethyl)phenyl	4.81	11.9	89

TABLE 4
Experimental Data for Tricylic Tetrahydroquinoline Controls

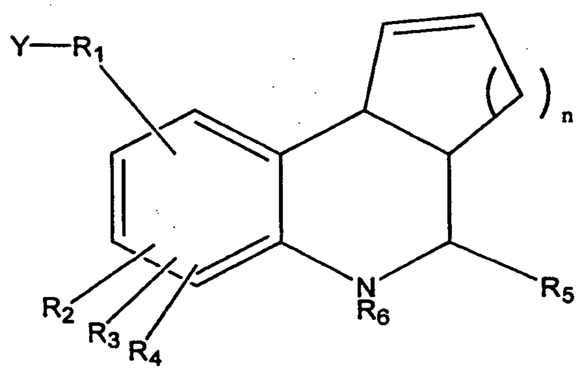
No.	2-Substituent (R^2)	HPLC RT (5 cm column)	Yield (mg)	Yield (%)
16	3,5-dichlorophenyl	4.7	13.1	112
17	3-cyanophenyl	3.83	13	123
18	3-fluorophenyl	4	11.4	110
19	3-formylchromone	3.74	11.4	98
20	3-nitro-4-chlorophenyl	4.26	13	109
21	3-phenoxyphenyl	4.57	10.9	89
22	4-cyanophenyl	4.97	6.3	60
23	4-pyridinecarboxaldehyde	0.33	9.6	96
24	3-methoxy-2-nitrophenyl	3.82	11.9	100
25	3-hydroxy-4-nitrophenyl	3.64	12.2	106

All journal article and reference citations provided above, in parentheses or otherwise, whether previously stated or not, are incorporated herein by reference.

Although the invention has been described with reference to the examples provided above, it should be understood that various modifications can be made by those skilled in the art without departing from the invention. Accordingly, the invention is set out in the following claims.

WE CLAIM:

1. A single tricyclic tetrahydroquinoline compound or a library of an approximately equimolar mixture of two or more compounds of the formula:



Formula I

wherein in the above Formula I:

R^1 is absent or present and, when present, is selected from the group consisting of C_1 to C_{10} alkylene, C_1 to C_{10} substituted alkylene, C_2 to C_{10} alkenyl, C_2 to C_{10} substituted alkenyl, C_2 to C_{10} alkynyl, C_2 to C_{10} substituted alkynyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, phenylene, substituted phenylene, naphthyl, substituted naphthyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, heterocyclic ring, substituted heterocyclic ring, heteroaryl ring, substituted heteroaryl ring, amino, (monosubstituted)amino, a group of the formula: $-CH_2C(O)NH-$ and a group of the formula:

$$-(CH_2)_p-Ar-(CH_2)_q-$$

wherein p and q are independently selected from a number 0 to 6, wherein both are not 0; and Ar is an aryl group selected from the group consisting of phenyl, substituted phenyl, heteroaryl ring and substituted heteroaryl ring,

R^2, R^3, and R^4 are, independently, selected from the group consisting of a hydrogen atom, halo, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_2 to C_{10} alkynyl, C_1 to C_{10} substituted alkyl, C_2 to C_{10} substituted alkenyl, C_2 to C_{10} substituted alkynyl, C_1 to C_7 alkoxy, C_1 to C_7 substituted alkoxy, C_1 to C_7 acyloxy, C_1 to C_7 acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, a heterocyclic ring, substituted heterocyclic ring, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, C_1 to C_4 alkylthio, C_1 to C_4 substituted alkylthio, C_1 to C_4 alkylsulfonyl, C_1 to C_4 substituted alkylsulfonyl, C_1 to C_4 alkylsulfoxide, C_1 to C_4 substituted alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl and substituted phenylsulfonyl;

R^5 is selected from the group consisting of hydrogen, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, C_2 to C_{10} alkenyl, C_2 to C_{10} substituted alkenyl, C_2 to C_{10} alkynyl, C_2 to C_{10} substituted alkynyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, carboxy, protected carboxy, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, heterocyclic ring, substituted heterocyclic ring, heteroaryl ring and substituted heteroaryl ring;

R^6 is selected from the group consisting of a hydrogen atom, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_4 alkylsulfonyl, C_1 to C_4 substituted alkylsulfonyl, C_1 to C_6 alkylaminocarbonyl, C_1 to C_6 substituted alkylaminocarbonyl, phenylaminocarbonyl, and substituted phenylaminocarbonyl;

n is 1 to 3; and

Y is selected from the group consisting of CO_2H, OH, SH, NHR^7, $C(O)NHR^7$, CH_2OH, CH_2NH_2, and CH_2NHR^7, wherein R^7 is selected from the group consisting of a hydrogen atom, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, and a functionalized resin, providing that when Y is CO_2H that R^1 is not absent and R^5 is not phenyl,

or a salt of the tricyclic tetrahydroquinoline.

2. A single tricyclic tetrahydroquinoline compound or a library of an approximately equimolar mixture of two or more compounds of claim 1, wherein:

R^1 is absent or present and, when present, is selected from the group consisting of C_1 to C_6 alkylene, C_1 to C_6 substituted alkylene, phenylene, substituted phenylene, and a group of the formula: $-CH_2C(O)NH-$;

R^2, R^3, and R^4 are, independently, selected from the group consisting of a hydrogen atom, halo, hydroxy, protected hydroxy, nitro, C_1 to C_{10} alkyl, C_1 to C_7 alkoxy, and cyclic C_2 to C_7 alkylene;

R^5 is selected from the group consisting of a hydrogen atom, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, C_2 to C_{10} alkenyl, C_2 to C_{10} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_3 to C_7 cycloalkyl, C_3 to C_7

substituted cycloalkyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_5 to C_7 cylcoalkenyl, C_5 to C_7 substituted cycloalkenyl, a heterocyclic ring, substituted heterocyclic ring, heteroaryl, substituted heteroaryl, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, carboxy, and protected carboxy;

R^6 is a hydrogen atom;

n is 1 to 2; and

Y is $C(O)NHR^7$, wherein R^7 is selected from the group consisting of a hydrogen atom and a functionalized resin.

3. A single tricyclic tetrahydroquinoline compound or a library of an approximately equimolar mixture of two or more compounds of claim 1, wherein:

R^1 is absent or present and, when present, is selected from the group consisting of $-CH_2C(O)NH-$ and $-CH_2CH(NHR^8)-$, wherein R^8 is selected from the group consisting of a hydrogen atom, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, C_2 to C_{10} alkenyl, C_2 to C_{10} substituted alkenyl, C_2 to C_{10} alkynyl, C_2 to C_{10} substituted alkynyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_7 acyl, C_1 to C_7 substituted acyl, aminocarbonyl, protected aminocarbonyl, (monosubstituted)aminocarbonyl, protected (monosubstitituted)aminocarbonyl, (disubstituted)aminocarbonyl, C_1 to C_7 alkylsulfonyl, C_7 to C_{12} phenylalkylsulfonyl, phenylsulfonyl, and substituted phenylsulfonyl;

R^2, R^3, and R^4 are each, independently, selected from the group consisting of a hydrogen atom, hydroxy, nitro, halo, C_1 to C_{10} alkyl, C_1 to C_6 alkoxy, and cyclic C_2 to C_7 alkylene;

R^5 is selected from the group consisting of a hydrogen atom, carboxy, C_1 to C_{10} alkyl, C_1 to C_{10} substituted alkyl, C_2 to C_{10} alkenyl, C_2 to C_{10} substituted alkenyl,

C_3 to C_8 cycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, heterocyclic ring, substituted heterocyclic ring, heteroaryl ring and substituted heteroaryl ring;

n is equal to 1;

R^6 is a hydrogen atom; and

Y is selected from the group consisting of $C(O)NH_2$ and C(O)NH bound to a functionalized resin.

4. A single tricyclic tetrahydroquinoline compound or a library of an approximately equimolar mixture of two or more compounds of claim 1, wherein:

R^1 is absent or $-CH_2NHCO-$;

R^2, R^3, and R^4 are each, independently, selected from the group consisting of a hydrogen atom, hydroxy, fluoro, chloro, bromo, iodo, methyl, methoxy, nitro and -CH=CH-CH=CH- fused to adjacent positions;

R^5 is selected from the group consisting of a hydrogen atom, phenyl, chloromethyl, cyclohexanyl, d,l- 1,2-(dihydroxy)ethyl, carboxy, acetyl, 2-hydroxyphenyl, tribromomethyl, trimethylacetyl, 1-methyl-2-pyrrolyl, 1-napthyl, 2,3,4-trifluorophenyl, 2,3,5-trichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-difluorophenyl, 2,5-dimethylphenyl, 2,6-difluorophenyl, 2-bromophenyl, 2-chloro-5-nitrophenyl, 2-chloro-6-fluorophenyl, 2-cyanophenyl, 2-ethylbutyryl, 2-fluorophenyl, 2-(2-oxymethylenecarboxy)phenyl, 2-methoxy-1-naphthyl, 2-nitro-5-chlorophenyl, 2-nitrophenyl, 2-pyridinyl, 3,4-(methylenedioxy)-6-nitrophenyl, 3,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-dichlorophenyl, 3-(3,4-dichlorophenoxy)phenyl, 3-bromo-4-fluorophenyl, 3-bromophenyl, 3-carboxyphenyl, 3-cyanophenyl, 3-fluorophenyl, 3-chromonyl, 3-

furyl, 3-hydroxyphenyl, 3-nitro-4-chlorophenyl, 3-nitrophenyl, 3-phenoxyphenyl, 2-phenylpropyl, 3-pyridinyl, 4-bromo-2-thiophene-yl, 4-bromophenyl, 4-carboxyphenyl, 4-cyanophenyl, 4-fluorophenyl, 4-nitrophenyl, 4-pyridinyl, 4-quinolinyl, 5-bromo-2-hydroxyphenyl, 5-nitro-2-furyl, 5-norbornene-2-yl, 6-methyl-2-pyridinyl, 9-ethyl-3-carbazolyl, 1,2-dimethylbutyryl, 1,1-dimethyl-3-butenyl, 3-methoxy-2-nitro-phenyl, 3-hydroxy-4-nitrophenyl, 1-methylpropyl, 1-methylbutyl, 4-chloro-3-nitrophenyl, 4-(trifluoromethyl)phenyl, 1-methyldecanyl, and β-phenylcinnaminyl;

R^6 is a hydrogen atom;

n is 1; and

Y is selected from the group consisting of $C(O)NH_2$ and C(O)NH bound to a functionalized resin.

5. A single tricyclic tetrahydroquinoline compound or a library of an approximately equimolar mixture of two or more compounds of claim 1, wherein:

R^1 is $CH_2CH(NHR^8)$, wherein R^8 is selected from the group consisting of acetyl, butyryl, cyclobutanecarbonyl, cycloheptanecarbonyl, 4-cyclohexanebutyryl, cyclohexanecarbonyl, 3-cyclohexanepropionyl, cyclohexylacetyl, cyclopentanecarbonyl, cyclopentylacetyl, hydrocinnamyl, isobutyryl, isovaleryl, octanoyl, propionyl, tert-butylacetyl, trimethylacetyl, 1-adamantaneacetyl, 4-methyl-1-cyclohexanecarbonyl, 4-methylcyclohexaneacetyl, 4-methylvaleryl, 2-ethyl-2-hexenoyl, 2-ethylbutyryl, 2-ethylhexanoyl, 2-methylbutyryl, 2-methylcyclopropanecarbonyl, 2-norbornaneacetyl, 2-phenylbutyryl, 2-propylpentanoyl, 3,3,3-triphenylpropionyl, 3,3-diphenylpropionyl, 4-tert-butyl-cyclohexanecarbonyl, 3,5,5-trimethylhexanoyl, 5-phenylvaleryl, 3-(2-methoxyphenyl)propionyl, 3-(3,4,5-trimethoxyphenyl)propionyl, 3-(3,4-dimethoxyphenyl)propionyl, heptanoyl, 3-cyclopentylpropionyl, formyl, lauryl,

3-methylvaleryl, 3-phenylbutyryl, α-cyclohexylphenylacetyl, α-methylcinnamyl, crotonyl, ethoxyacetyl, 4-chlorocinnamyl, 4-ethoxyphenylacetyl, m-tolylacetyl, methoxyacetyl, p-tolylacetyl, phenoxyacetyl, phenylacetyl, tiglyl, trans-3-hexenoyl, trans-cinnamyl, trans-styrylacetyl, triphenylacetyl, 4-fluorophenylacetyl, vinylacetyl, (2,5-dimethoxyphenyl)acetyl, (2-naphthoxy)acetyl, (3,4-dimethoxyphenyl)acetyl, (α-α-α-trifluoro-m-tolyl)acetyl, (methylthio)acetyl, 1-(4-chlorophenyl)-1-cyclopentanecarbonyl, 1-naphthylacetyl, 1-phenyl-1-cyclopropanecarbonyl, 4-isobutyl-α-methylphenylacetyl, 4-methoxyphenylacetyl, 2,4-hexadienoyl, 2-(trifluoromethyl)-cinnamyl, 2-chloro-4-fluorophenylacetyl, 2-naphthylacetyl, 3,4,5-trimethoxycinnamyl, 3,4-dichlorophenylacetyl, 3,4-dimethylbenzoyl, 3,4,5-trimethoxyphenylacetyl, 3-benzoylpropionyl, 3-bromophenylacetyl, 3-fluorophenylacetyl, 3-methoxyphenylacetyl, 3-thiopheneacetyl, 4-biphenylacetyl, 4-bromophenylacetyl, α,α,α-trifluoro-m-toluyl, α,α,α-trifluoro-o-toluyl, benzoyl, niflumyl, o-anisyl, o-toluyl, piperonylyl, 1-napthoyl, 2,3-dichlorobenzoyl, 2,3-dimethoxybenzoyl, 2,4-dichlorobenzoyl, 2,4-difluorobenzoyl, 2,4-dimethoxybenzoyl, 2,4-dimethylbenzoyl, 2,5-dichlorobenzoyl, 2,5-dimethylbenzoyl, 2,6-dychlorobenzoyl, 2,6-difluorobenzoyl, 2,6-dimethoxybenzoyl, 2-bromobenzoyl, 2-chloro-4,5-difluorobenzoyl, 2-chlorobenzoyl, 2-ethoxybenzoyl, 2-fluorobenzoyl, 2-napthoyl, 3,4,5-triethoxybenzoyl, 3,4,5-trimethoxybenzoyl, 3,4-dichlorobenzoyl, 3,4-difluorobenzoyl, 3,4-dimethoxybenzoyl, 3,5-bis(trifluoromethyl)benzoyl, 5-bromo-2-chlorobenzoyl, 3,5-dimethyl-p-anisyl, 3-bromobenzoyl, 3-chlorobenzoyl, 3-cyanobenzoyl, 3-(dimethylamino)benzoyl, 3-fluoro-4-methylbenzoyl, 3-fluorobenzoyl, 3-iodo-4-methylbenzoyl, 3-phenoxybenzoyl, 4-chloro-o-anisyl, α,α,α-trifluoro-p-toluyl, 4-cyanobenzoyl, 4-(dimethylamino)benzoyl, 4-ethoxybenzoyl, isonicotinyl, 4-ethylbenzoyl, m-anisyl, m-toluyl, nicotinyl, p-anisyl, p-toluyl, picolinyl, pyrrole-2-carbonyl, 4-fluorobenzoyl, 4-isopropoxybenzoyl, tetrahydro-2-furoyl, tetrahydro-3-furoyl, trans-3-(3-pyridyl)acrylyl, xanthene-9-carbonyl, (4-pyridylthio)acetyl, (phenylthio)acetyl, 4-iodobenzoyl, 4-isopropylbenzoyl, 2-furoyl, 2-

pyrazinecarbonyl, 2-thiopheneacetyl, 2-thiophenecarbonyl, 5-bromonicotinyl, 3,5-dichlorobenzoyl, 6-chloronicotinyl, 3,5-dimethoxybenzoyl, 3,5-dimethylbenzoyl, chromone-2-carbonyl, 1-isoquinolinecarbonyl, 3-methyl-2-thiophene-yl, 4'-ethyl-4-biphenylcarbonyl, 4-(diethylamino)benzoyl, 4-benzoylbenzoyl, 4-biphenylcarbonyl, 4-bromobenzoyl, 4-butylbenzoyl, and 4-chlorobenzoyl;

R^2, R^3, and R^4 are each, independently, a hydrogen atom;

R^5 is selected from the group consisting of carboxy, 1-napthyl, 2,3,4-trifluorophenyl, 2,3,5-trichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-difluorophenyl, 2,5-dimethylphenyl, 2,6-difluorophenyl, 2-bromophenyl, 2-chloro-5-nitrophenyl, 2-fluorophenyl, 3,4-(methylenedioxy)-6-nitrophenyl, 3,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-dichlorophenyl, 3-cyanophenyl, 3-fluorophenyl, 3-chromonyl, 3-nitro-4-chlorophenyl, 3-phenoxyphenyl, 4-cyanophenyl, 4-pyridinyl, 3-methoxy-2-nitrophenyl, and 3-hydroxy-4-nitrophenyl;

R^2, R^3, and R^4 are each, independently, a hydrogen atom;

R^5 is selected from the group consisting of carboxy, 1-napthyl, 2,3,4-trifluorophenyl, 2,3,5-trichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-difluorophenyl, 2,5-dimethylphenyl, 2,6-difluorophenyl, 2-bromophenyl, 2-chloro-5-nitrophenyl, 2-fluorophenyl, 3,4-(methylenedioxy)-6-nitrophenyl, 3,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-dichlorophenyl, 3-cyanophenyl, 3-fluorophenyl, 3-chromonyl, 3-nitro-4-chlorophenyl, 3-phenoxyphenyl, 4-cyanophenyl, 4-pyridinyl, 3-methoxy-2-nitrophenyl, and 3-hydroxy-4-nitro-phenyl,

R^6 is a hydrogen atom;

n is 1; and

Y is selected from the group consisting of $C(O)NH_2$ and C(O)NH bound to a functionalized resin.

6. A single tricyclic tetrahydro-quinoline compound or a library of an approximately equimolar mixture of two or more compounds of claim 1, wherein:

R^1 is absent or present and, when present, is selected from the group consisting of -CH_2NHCO- and $CH_2CH(NHR^8)$ wherein R^8 is selected from the group consisting of acetyl, butyryl, cyclobutanecarbonyl, cycloheptanecarbonyl, 4-cyclohexanebutyryl, cyclohexanecarbonyl, 3-cyclohexanepropionyl, cyclohexylacetyl, cyclopentanecarbonyl, cyclopentylacetyl, hydrocinnamyl, isobutyryl, isovaleryl, octanoyl, propionyl, tert-butylacetyl, trimethylacetyl, 1-adamantaneacetyl, 4-methyl-1-cyclohexanecarbonyl, 4-methylcyclohexaneacetyl, 4-methylvaleryl, 2-ethyl-2-hexenoyl, 2-ethylbutyryl, 2-ethylhexanoyl, 2-methylbutyryl, 2-methylcyclopropanecarbonyl, 2-norbornaneacetyl, 2-phenylbutyryl, 2-propylpentanoyl, 3,3,3-triphenylpropionyl, 3,3-diphenylpropionyl, 4-tert-butyl-cyclohexanecarbonyl, 3,5,5-trimethylhexanoyl, 5-phenylvaleryl, 3-(2-methoxyphenyl)propionyl, 3-(3,4,5-trimethoxyphenyl)propionyl, 3-(3,4-dimethoxyphenyl)propionyl, heptanoyl, 3-cyclopentylpropionyl, formyl, lauryl, 3-methylvaleryl, 3-phenylbutyryl, α-cyclohexylphenylacetyl, α-methylcinnamyl, crotonyl, ethoxyacetyl, 4-chlorocinnamyl, 4-ethoxyphenylacetyl, m-tolylacetyl, methoxyacetyl, p-tolylacetyl, phenoxyacetyl, phenylacetyl, tiglyl, trans-3-hexenoyl, trans-cinnamyl, trans-styrylacetyl, triphenylacetyl, 4-fluorophenylacetyl, vinylacetyl, (2,5-dimethoxyphenyl)acetyl, (2-naphthoxy)acetyl, (3,4-dimethoxyphenyl)acetyl, (α-α-α-trifluoro-m-tolyl)acetyl, (methylthio)acetyl, 1-(4-chlorophenyl)-1-cyclopentanecarbonyl, 1-naphthylacetyl, 1-phenyl-1-cyclopropanecarbonyl, 4-isobutyl-α-methylphenylacetyl, 4-methoxyphenylacetyl, 2,4-hexadienoyl, 2-(trifluoromethyl)-cinnamyl, 2-chloro-

4-fluorophenylacetyl, 2-naphthylacetyl, 3,4,5-trimethoxycinnamyl, 3,4-dichlorophenylacetyl, 3,4-dimethylbenzoyl, 3,4,5-trimethoxyphenylacetyl, 3-benzoylpropionyl, 3-bromophenylacetyl, 3-fluorophenylacetyl, 3-methoxyphenylacetyl, 3-thiopheneacetyl, 4-biphenylacetyl, 4-bromophenylacetyl, α,α,α-trifluoro-m-toluyl, α,α,α-trifluoro-o-toluyl, benzoyl, niflumyl, o-anisyl, o-toluyl, piperonylyl, 1-napthoyl, 2,3-dichlorobenzoyl, 2,3-dimethoxybenzoyl, 2,4-dichlorobenzoyl, 2,4-difluorobenzoyl, 2,4-dimethoxybenzoyl, 2,4-dimethylbenzoyl, 2,5-dichlorobenzoyl, 2,5-dimethylbenzoyl, 2,6-dychlorobenzoyl, 2,6-difluorobenzoyl, 2,6-dimethoxybenzoyl, 2-bromobenzoyl, 2-chloro-4,5-difluorobenzoyl, 2-chlorobenzoyl, 2-ethoxybenzoyl, 2-fluorobenzoyl, 2-napthoyl, 3,4,5-triethoxybenzoyl, 3,4,5-trimethoxybenzoyl, 3,4-dichlorobenzoyl, 3,4-difluorobenzoyl, 3,4-dimethoxybenzoyl, 3,5-bis(trifluoromethyl)benzoyl, 5-bromo-2-chlorobenzoyl, 3,5-dimethyl-p-anisyl, 3-bromobenzoyl, 3-chlorobenzoyl, 3-cyanobenzoyl, 3-(dimethylamino)benzoyl, 3-fluoro-4-methylbenzoyl, 3-fluorobenzoyl, 3-iodo-4-methylbenzoyl, 3-phenoxybenzoyl, 4-chloro-o-anisyl, α,α,α-trifluoro-p-toluyl, 4-cyanobenzoyl, 4-(dimethylamino)benzoyl, 4-ethoxybenzoyl, isonicotinyl, 4-ethylbenzoyl, m-anisyl, m-toluyl, nicotinyl, p-anisyl, p-toluyl, picolinyl, pyrrole-2-carbonyl, 4-fluorobenzoyl, 4-isopropoxybenzoyl, tetrahydro-2-furoyl, tetrahydro-3-furoyl, trans-3-(3-pyridyl)acrylyl, xanthene-9-carbonyl, (4-pyridylthio)acetyl, (phenylthio)acetyl, 4-iodobenzoyl, 4-isopropylbenzoyl, 2-furoyl, 2-pyrazinecarbonyl, 2-thiopheneacetyl, 2-thiophenecarbonyl, 5-bromonicotinyl, 3,5-dichlorobenzoyl, 6-chloronicotinyl, 3,5-dimethoxybenzoyl, 3,5-dimethylbenzoyl, chromone-2-carbonyl, 1-isoquinolinecarbonyl, 3-methyl-2-thiophene-yl, 4'-ethyl-4-biphenylcarbonyl, 4-(diethylamino)benzoyl, 4-benzoylbenzoyl, 4-biphenylcarbonyl, 4-bromobenzoyl, 4-butylbenzoyl, and 4-chlorobenzoyl;

R^2, R^3, and R^4 are each, independently, selected from the group consisting of a hydrogen atom, hydroxy, fluoro, chloro, bromo, iodo, methyl, methoxy, nitro and -CH=CH-CH=CH- fused to adjacent positions;

R^5 is selected from the group consisting of a hydrogen atom, phenyl, chloromethyl, cyclohexanyl, d,l- 1,2-(dihydroxy)ethyl, carboxy, acetyl, 2-hydroxyphenyl, tribromomethyl, trimethylacetyl, 1-methyl-2-pyrrolyl, 1-napthyl, 2,3,4-trifluorophenyl, 2,3,5-trichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-difluorophenyl, 2,5-dimethylphenyl, 2,6-difluorophenyl, 2-bromophenyl, 2-chloro-5-nitrophenyl, 2-chloro-6-fluorophenyl, 2-cyanophenyl, 2-ethylbutyryl, 2-fluorophenyl, 2-(2-oxymethylenecarboxy)phenyl, 2-methoxy-1-naphthyl, 2-nitro-5-chlorophenyl, 2-nitrophenyl, 2-pyridinyl, 3,4-(methylenedioxy)-6-nitrophenyl, 3,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-dichlorophenyl, 3-(3,4-dichlorophenoxy)phenyl, 3-bromo-4-fluorophenyl, 3-bromophenyl, 3-carboxyphenyl, 3-cyanophenyl, 3-fluorophenyl, 3-chromonyl, 3-furyl, 3-hydroxyphenyl, 3-nitro-4-chlorophenyl, 3-nitrophenyl, 3-phenoxyphenyl, 2-phenylpropyl, 3-pyridinyl, 4-bromo-2-thiophene-yl, 4-bromophenyl, 4-carboxyphenyl, 4-cyanophenyl, 4-fluorophenyl, 4-nitrophenyl, 4-pyridinyl, 4-quinolinyl, 5-bromo-2-hydroxyphenyl, 5-nitro-2-furyl, 5-norbornene-2-yl, 6-methyl-2-pyridinyl, 9-ethyl-3-carbazolyl, 1,2-dimethylbutyryl, 1,1-dimethyl-3-butenyl, 3-methoxy-2-nitro-phenyl, 3-hydroxy-4-nitrophenyl, 1-methylpropyl, 1-methylbutyl, 4-chloro-3-nitrophenyl, 4-(trifluoromethyl)phenyl, 1-methyldecanyl, and β-phenylcinnaminyl;

R^6 is selected from the group consisting of nalidixoyl, 2-phenyl-4-quinolinecarboxy, 2-pyrazinecarboxy, niflumoyl, 4-nitrophenylacetyl, 4-(4-nitrophenyl)butyroyl, (3,4-dimethoxyphenyl)-acetyl, 3,4-(methylenedioxy)phenylacetyl, 4-nitrocinnamoyl, 3,4,-(methylenedioxy)cinnamoyl, 3,4,5-trimethoxycinnamoyl, benzoyl, 2-chlorobenzoyl, 2-nitrobenzoyl, 2-(p-toluoyl)benzoyl, 2,4-dinitrophenylacetyl, 3-(3,4,5-trimethoxyphenyl)-propionyl, 4-biphenylacetyl, 1-napthylacetyl,

(2-napthoxy)acetyl, trans-cinnamoyl, picolinyl, 3-amino-4-hydroxybenzoyl, (4-pyridylthio)acetyl, 2,4-dichlorobenzoyl, 3,4-dichlorobenzoyl, 4-biphenylcarboxy, thiophenoxyacetyl, 1-benzoylpropionyl, phenylacetyl, hydrocinnamoyl, 3,3-diphenylpropionyl, 3,3,3-triphenylpropionyl, 4-phenylbutyryl, phenoxyacetyl, (+/-)-2-phenoxypropionyl, 2,4-dimethoxybenzoyl, 3,4-dimethoxybenzoyl, 3,4-dihydroxybenzoyl, 2,4-dihydroxybenzoyl, 3,4,5-trimethoxybenzoyl, 3,4,5-triethoxybenzoyl, 3,4,5-trihydroxybenzoyl, 2-benzoylbenzoyl, 1-napthoyl, xanthene-9-carboxy, 4-chloro-2-nitrobenzoyl, 2-chloro-4-nitrobenzoyl, 4-chloro-3-nitrobenzoyl, 2-chloro-5-nitrobenzoyl, 4-(dimethylamino)benzoyl, 4-(diethylamino)benzoyl, 4-nitrobenzoyl, 3-(dimethylamino)benzoyl, p-methylbenzoyl, p-methoxybenzoyl, trimethylacetyl, tert-butylacetyl, (-)-menthoxyacetyl, cyclohexanecarboxy, cyclohexylacetyl, dicyclohexylacetyl, 4-cyclohexylbutyroyl, cycloheptanecarboxy, 13-isopropylpodocarpa-7,13-dien-15-oyl, acetyl, octanoyl, (methylthio)acetyl, 3-nitropropionyl, 4-amino-3 hydroxybenzoyl, 3-(2-methyl-4-nitro-1-imidizoyl)propionyl, 2-furoyl, (s)(-)-2-pyrrolidone-5-carboxy, (2-pyrimidylthio)acetyl, 4-methoxy-2-quinolinecarboxy, 1-adamantanecarboxy, piperonoyl, 5-methyl-3-phenylisoxazole-4-carboxy, rhodanine-3-acetyl, 2-norbornaneacetyl, nicotinoyl, 9-oxo-9H-thioxanthene-3-carboxyl-10,10 dioxide, 2-thiophenecarboxy, 5-nitro-2-furanoyl, indole-3-acetyl, isonicotinoyl, 3α-hydroxy-5β-cholan-24-oyl, (3α,7α,12α)-trihydroxy-5β-cholan-24-oyl, (3α, 5β-12α)-3,12, dihydroxy-5-cholan-24-oyl, (3α, 5β, 6α)-3,6-dihydroxy-cholan-24-oyl, L-alaninyl, L-cysteinyl, L-aspartinyl, L-glutaminyl, L-phenylalaninyl, glycinyl, L-histidinyl, L-isoleucinyl, L-lyscinyl, L-leucinyl, L-methionylsulfoxide, L-methionyl, L-asparginyl, L-prolinyl, L-glutaminyl, L-arganinyl, L-serinyl, L-threoninyl, L-valinyl, L-tryptophanoyl, L-tyrosinyl, D-alaninyl, D-cysteinyl, D-aspartinyl, D-glutaminyl, D-phenylalaninyl, glycinyl, D-histidinyl, D-isoleucinyl, D-lyscinyl, D-leucinyl, D-methionylsulfoxide, D-methionyl, D-asparginyl, D-prolinyl, D-glutaminyl, D-arganinyl, D-serinyl, D-threoninyl, D-valinyl, D-tryptophanoyl, D-tyrosinyl, 2-aminobutyroyl,

4-aminobutyroyl, 2-aminoisobutyroyl, L-norleucinyl, D-norleucinyl, 6-aminohexanoyl, 7-aminoheptanoyl, thioprolinyl, L-norvalinyl, D-norvalinyl, α-ornithinyl, methionyl sulfonyl, L-naphthylalaninyl, D-naphthylalaninyl, L-phenylglycinyl, D-phenylglycinyl, ß-alaninyl, L-cyclohexylalaninyl, D-cyclohexylalaninyl, hydroxyprolinyl, 4-nitrophenylalaninyl, dehydroprolinyl, 3-hydroxy-1-propanesulfonyl, 1-propanesulfonyl, 1-octanesulfonyl, perfluoro-1-octanesulfonly, (+)-10-camphorsulfonyl, (-)-10-camphorsulfonyl, benzenesulfonyl, 2-nitrobenzenesulfonyl, p-toluenesulfonyl, 4-nitrobenzenesulfonyl, n-acetylsulfanilyl, 2,5-dichlorobenzenesulfonyl, 2,4-dinitrobenzenesulfonyl, 2-mesitylenesulfonyl and 2-napthalenesulfonyl;

n is 1; and

Y is selected from the group consisting of $C(O)NH_2$ and C(O)NH bound to a functionalized resin.

7. A combinatorial library, comprising a plurality of mixtures of the tetrahydroquinoline compounds of claim 1, wherein within each of the mixtures all the compounds have at least one substituent in common, wherein the substituent is selected from the group consisting of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and Y, with the proviso that not all of the substituents are in common and that all other noncommon substituents are present as equimolar mixtures.

8. A method for the preparation of a library of two or more tricyclic tetrahydroquinoline compounds of claim 1, comprising the following steps:

(a) reacting a resin-bound aniline with an aldehyde to obtain an imine; and

(b) reacting, in the presence of an acid, the imine of step (a) with a dienophile to yield a tetrahydroquinoline.

9. A method for the preparation of a library of two or more tricyclic tetrahydroquinoline compounds of claim 1, comprising the following steps:

(a) reducing the nitro group of a resin-bound substituted- or protected-amino-nitroaryl species to produce an aniline;

(b) reacting the resin-bound aniline with an aldehyde to obtain an imine; and

(c) reacting, in the presence of an acid, the imine of step (b) with a dienophile to yield a tetrahydroquinoline.

10. The method of claim 8, further comprising the step of cleaving the tricyclic tetrahydroquinoline from the resin.

11. The method of claim 9, further comprising the step of cleaving the tricyclic tetrahydroquinoline from the resin.

12. The method of claim 8, wherein the library contains a plurality of mixtures of the tricyclic tetrahydroquinoline compounds and further where in each mixture all compounds of the mixture have at least one substituent in common, wherein the substituent is selected from the group consisting of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and Y, with the proviso that not all the substituents are in common and that all other noncommon substituents are present as equimolar mixtures.

13. The method of claim 9, wherein the library contains a plurality of mixtures of the tricyclic tetrahydroquinoline compounds and further where in each mixture all compounds of the mixture have at least one substituent in common, wherein the substituent is selected from the group consisting of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and Y, with the proviso that not all the substituents are in common and that all other noncommon substituents are present as equimolar mixtures.

14. The method of claim 8, further comprising the step of condensing the tricyclic tetrahydroquinolineresulting from step 8(b) with a reagent selected from the groups consisting of carboxylic acid, carboxylic acid anhydride, acid halide, alkyl halide and isocyanate.

15. The methods of claim 9, further comprising the step of condensing the ttricyclic tetrahydroquinolineresulting from step 9(c) with a reagent selected from the group consisting of carboxylic acid, carboxylic acid anhydride, acid halide, alkyl halide and isocyanate.

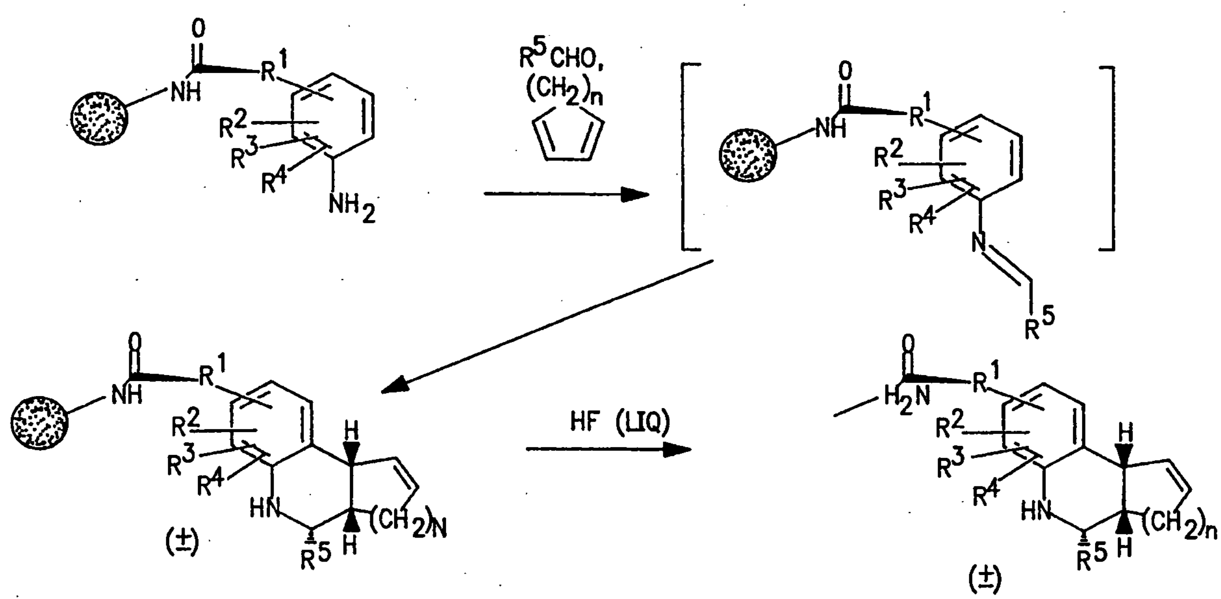

O
NH
R1
R2
R3
R4
NH2
R5CHO,
(CH2)n
O
NH
R1
R2
R3
R4
N
R5
O
NH
R1
R2
R3
R4
HN
R5
H
H
(CH2)N
(±)
HF (LIQ)
O
H2N
R1
R2
R3
R4
HN
R5
H
H
(CH2)n
(±)

FIG. 1

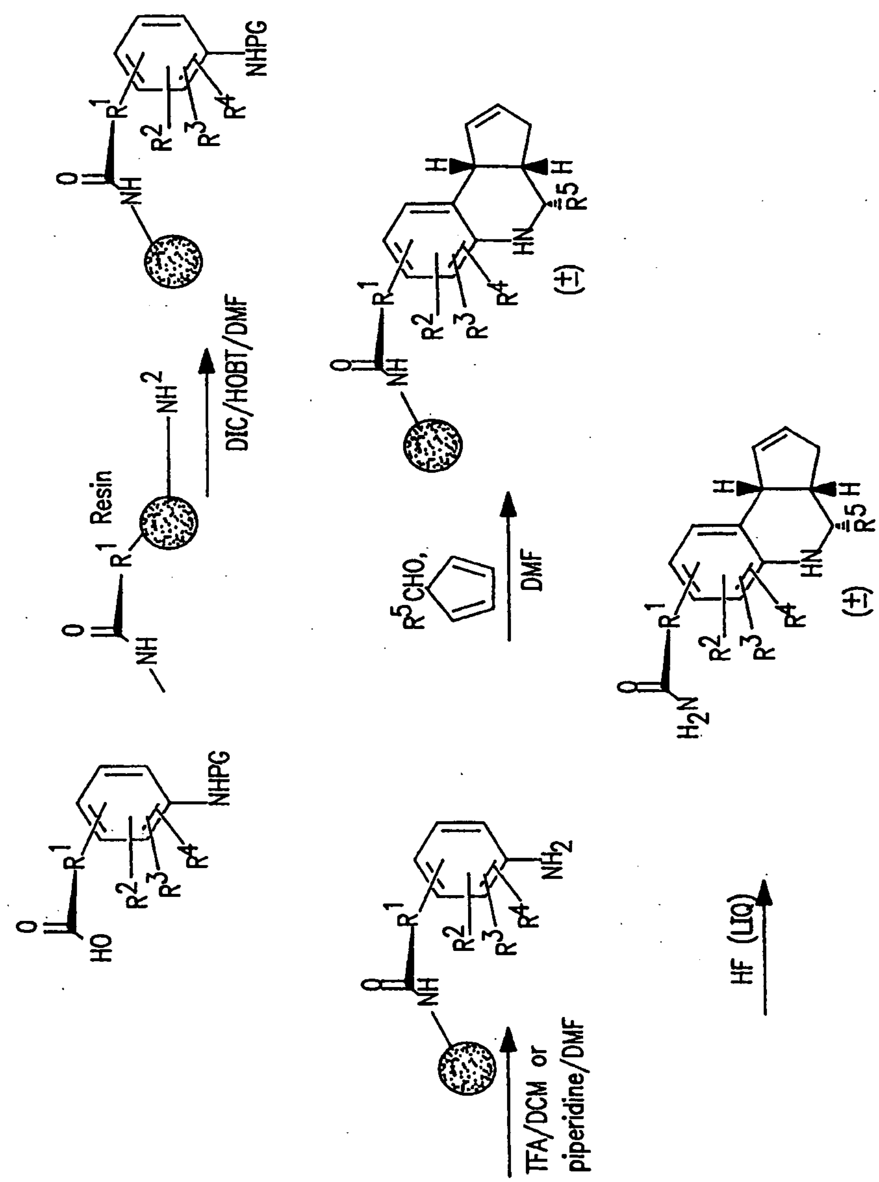
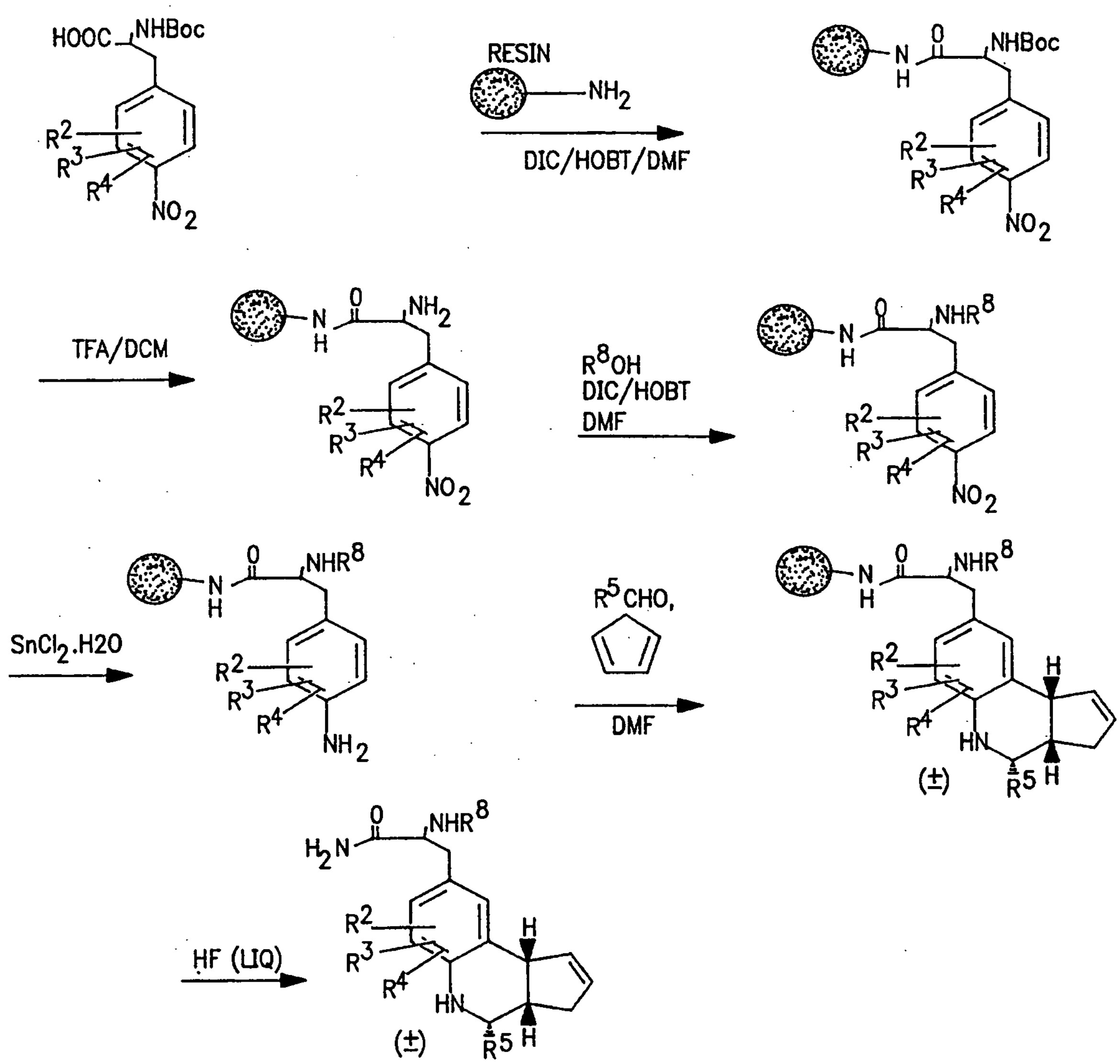


FIG. 2



HOOC
NHBoc
R^2
R^3
R^4
NO_2
RESIN
NH_2
DIC/HOBT/DMF
TFA/DCM
R^8OH
DIC/HOBT
DMF
NHR^8
$SnCl_2.H2O$
$R^5CHO,$
DMF
HN
(±)
$R5$
HF (LIQ)
H_2N

FIG. 3

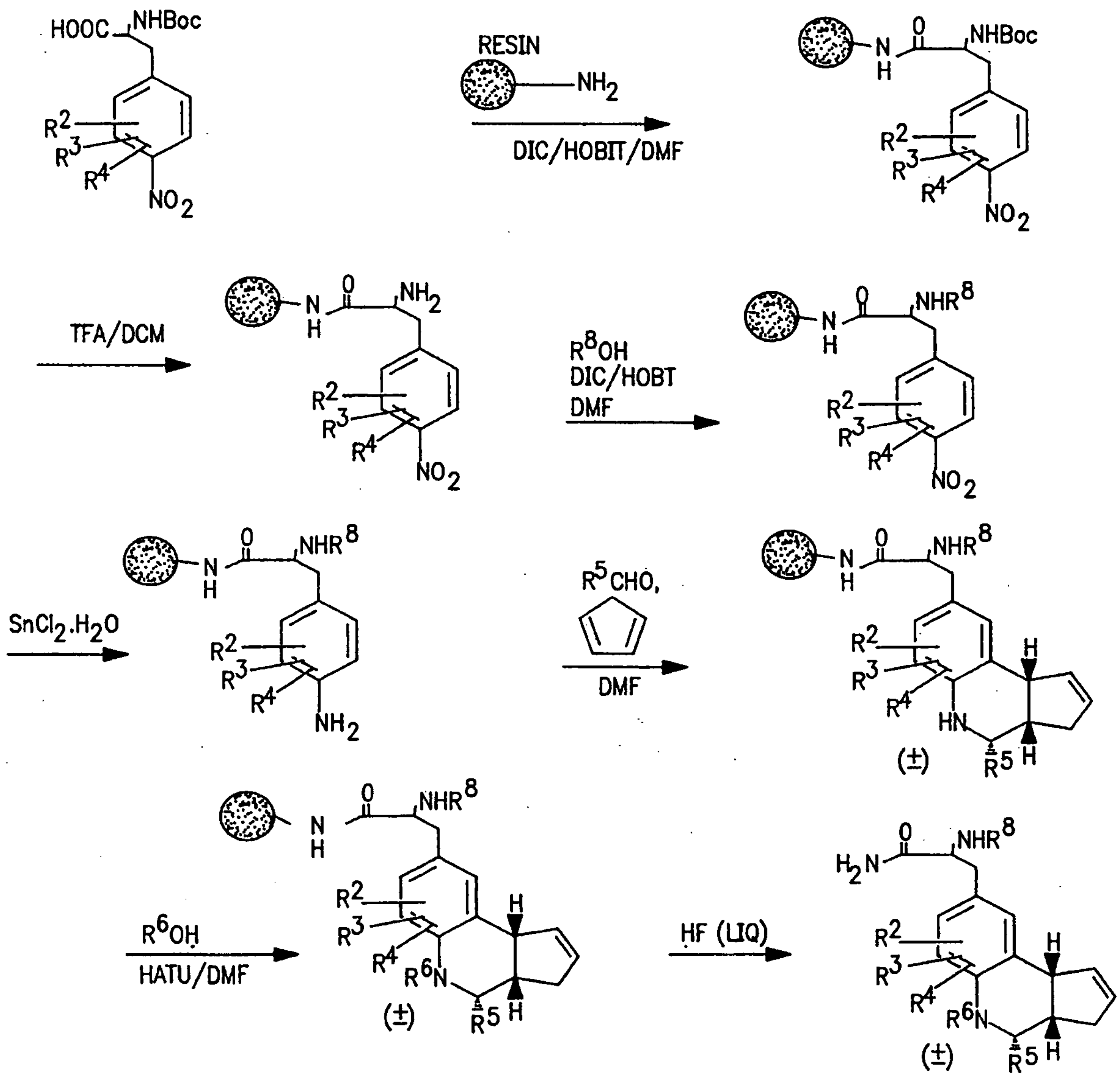

HOOC NHBoc
R^2
R^3
R^4
NO_2
RESIN
NH_2
DIC/HOBIT/DMF
N H O NHBoc
TFA/DCM
NH_2
R^8OH
DIC/HOBT
DMF
NHR^8
$SnCl_2.H_2O$
R^5CHO,
DMF
H
HN
(±)
R^5
R^6OH
HATU/DMF
R^6N
HF (LIQ)
H_2N

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/22206

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :G01N 33/53
US CL :435/7.1; 436/501, 518
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/7.1; 436/501, 518

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS, STN
search terms: structure search, tetrahydroquinoline, library, combinatorial

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y --- A	LUCCHINI et al. Cycloaddition Reactions of Ketoimines. Part II. Synthesis of Substituted Phenanthridines and Cyclopenta[c]quinolines [1]. J. Heterocyclic Chem. 1986. Vol. 23. pages 1135-1139, see especially page 1135.	1 --- 2-7 --- 8-15
Y --- A	GORDON et al. Applications of Combinatorial Technologies to Drug Discovery. 2. Combinatorial Organic Synthesis, Library Screening Strategies, and Future Directions. 13 May 1994. Vol. 37. No. 10. pages 1335-1401, see entire article.	1-7 --- 8-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document published on or after the international filing date
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- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 FEBRUARY 1998	13 MAR 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Deborah Freese for LORA M. GREEN Telephone No. (703) 308-0196